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SOME EFFECTS OF SOAP ON THE SKIN*

BY

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Views on the action of soap on the skin have changed a good deal in the past; to the Victorians cleanliness came next to godliness, and the consumption of soap in this country increased enormously with advances in chemical techniques of the industrial revolution. Pears soap carried the testimonial of three prominent dermatologists in concert—Erasmus Wilson, James Startin, and John Milton, the founder of St. John's Hospital for Diseases of the Skin. I do not suppose that the nature of soap has changed much since their time, but knowledge of its action on the skin has broadened and the whole position has now altered in that other cleansers are available and the use of soap is not the only alternative to squalor.

The enthusiastic support of soap accorded by the Victorians was followed by a reactionary swing, and some senior dermatologists between the wars considered it almost wholly bad. Henry MacCormac, for example, used to attribute to soap far more harm than good in the cause and prevention of skin diseases. To-day we have perhaps a position somewhere between these two extremes.

Antibacterial Action

Though it is not my purpose to consider at length the cleansing power of soap on the skin, it may be appropriate to mention its effect on the bacterial flora. The antibacterial action of soap was investigated and described by Walker (1924, 1925, 1926). He found that the antiseptic action varied with the soap according to its fatty-acid content and with the bacteria studied. Thus, oleate and linoleate had negligible action in respect of *Salmonella typhi* but were effective against pneumococci; palmitate and stearate soaps were effective against both organisms. The mixed soaps sold commercially contain a variety of fatty acids which should give them good antiseptic action against streptococci, pneumococci, *Corynebacterium diphtheriae*, meningococci, and gonococci. The Gram-negative rods *Escherichia coli*, *Salm typhi*, and the paratyphoid group are more resistant. In these days it is particularly important to observe that *Staphylococcus aureus* appears to be completely resistant to soap. Colebrook and Maxted (1933) confirmed some of these results and found that in respect of streptococci the antiseptic action of 1 in 400 soap solution was greater than that of 1 in 160 lysol or 1 in 1,000 mercury perchloride.

Perhaps more important than killing micro-organisms is their removal from the skin by washing. Colebrook and Maxted deposited cultures and infected secretions on the skin and under various conditions attempted to recover them later by swabbing. They found that five minutes' ordinary washing was apparently sufficient to remove contamination with streptococci but not with staphylococci—that is to say, they could no longer recover the test organisms after washing. Price (1938) used a standardized technique by which hands and forearms were scrubbed with soap and water for one minute in 14 consecutive bowls. After cultures of the washing water had been examined, the total number of bacteria removed in each washing was calculated, and from this an estimate was made of the total number of micro-organisms which had been present on the skin surface. As might be expected, the number of organisms removed by each successive washing becomes less and less. Price estimated that about half the total flora are removed in the first six minutes and two-thirds in the first ten minutes.

The whole bacterial flora are never removed, and this led to Price's conception of resident and transient flora. The former are fortunately usually not pathogenic, though sometimes a pathogen may become installed as a resident. According to Pohle and Stuart (1940) *Staph. albus* is the most common resident; Pillsbury *et al.* (1942) also identified a coagulase-negative *Staph. aureus*, *Micrococcus luteus*, *M. epidermidis*, and others. They found that even after 10 to 12 washings these organisms continued to appear in the washing-water, and all these authors have concluded that it is not possible to remove all the bacteria from the skin surface by washing.

The transient flora are those which are deposited on the skin and which are, apart from washing, at the peril of the self-sterilizing power of the skin. Following the work of Colebrook and Maxted, Price also decided that the transient organisms were easily removed by washing, especially if they were not allowed to remain long on the skin. Their results indicate that, in practice, when the hands are recently contaminated by handling infected material they can be easily cleaned and pathogenic organisms removed by thorough washing with ordinary non-medicated soap.

Property of Cleansing

The property of cleansing or detergency is not altogether straightforward, and in the dermatological literature at least is not well defined. To remove water-soluble dirt a sufficient quantity of water is presumably all that is required. For oily or greasy dirt the usual fat solvents could be used. These are not, however, suitable for repeated application to the skin, and the alternative is to remove fatty material by emulsifying it.

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Skin cleansers are therefore surface-active substances, emulsifiers which lower surface tension at the oil-water interface and bring grease away from the skin in an emulsified form. The removal of insoluble dirt particles, including bacteria, is sometimes said to result from merely floating them off the skin, as the skin and the foreign bodies are more readily wetted by a low-surface-tension aqueous solution. This explanation is not enough.

McBain (1920) stressed the importance of the colloidal nature of soap solution and attributed the removal of solid dirt particles to the formation of sorption compounds with soap molecules. He quotes Shorter as mentioning that, in the presence of alkali, dirt particles and the surface to be cleansed both carry a negative charge. Lane and Blank (Fishbein, 1945) quote evidence that at a *p*H above its isoelectric point keratin carries an increasingly negative charge. Most solid dirt particles and bacteria are also negatively charged, so that they are actively repelled from the keratin surface in the presence of an alkali, but are attracted and held to the skin at an acid *p*H, when the skin surface is positively charged. Blank and Coolidge (1950) confirmed these findings in respect of human keratin.

The active part of the soap molecule, the fatty-acid anion, also bears a negative charge ; hence it is repelled by the skin surface and remains free in the solute. In the case of cationic detergents, such as the quaternary ammonium compounds, the surface-active cation is attracted to the keratin and adsorbed on to the skin surface, with consequent loss of detergent power. It appears from this that the most efficient cleanser for the skin should be an anionic detergent and should be alkaline. Ordinary soap, of course, fulfils this requirement ; and the alkalinity of soap, which is so often regarded as a disadvantage, in fact makes a valuable contribution to its cleansing power on the skin. The keratin, surface-active anion, and the solid dirt or bacteria will then all bear negative charges and will repel each other.

As Blank and Coolidge point out, this has an important bearing on investigations into the degerming (killing and removal of bacteria) of the skin. Many of these investigations have assumed that the number of organisms which can be removed from the skin surface is a direct indication of the number present. When it is now appreciated that the ease of removal is greatly influenced by *p*H and by the nature of the cleanser, this assumption seems to be unjustified and some of this work therefore may need to be reassessed.

One may also observe that the efficiency of a cleanser will depend upon the nature of the surface to be cleansed. Keratin, a protein with an isoelectric point of 3.5 to 5.5, is clearly very different from cotton, nylon, and crockery. This point is of importance not only to achieve efficiency and economy in cleansing, but, by choosing cleansers where possible which have little effect on the skin, to minimize the risk of irritant effects.

Self-sterilizing Power of the Skin

We must also consider the possible effect of washing on the self-sterilizing power of the skin. It has for many years been held that organisms deposited on the living skin are likely to die more quickly than if they are placed under comparable conditions on an inanimate surface. Even the skin of a cadaver loses its sterilizing power as soon as 15 minutes after death (Arnold *et al.*, 1930). They concluded that the acid *p*H of the normal skin was important for this function. However, Cornbleet (1933) found that staphylococci survived indefinitely in thermal sweat at *p*H down to 3, but that a skin surface at *p*H 7 inactivated those organisms. Burtenshaw (1948) found that fat-soluble extracts of skin were strongly bactericidal, especially the fatty acid and soap fractions. The bactericidal action of these substances may depend, as Walker suggested, not upon *p*H but upon the lowering of interface tension on the surface of the bacterium.

Washing with soap removes these substances from the skin and raises the *p*H but tends to leave behind a deposit of the soap (Ramsay and Jones, 1955) which may in some degree make up for the loss. Rebell *et al.* (1950) found that the self-sterilizing power of the skin was greatly decreased if the surface lipoids were removed with ether, but I am unable to find any report of investigations into the self-sterilizing power of the skin after it has been washed with soap. The results would be interesting and possibly important, for these various effects of washing with soap are antagonistic. One may observe in passing that furunculosis commonly affects chiefly the areas of skin which are washed most frequently and that the avoidance of shaving-soap is often sufficient to cure folliculitis of the beard region ; similar considerations apply to chronic paronychia, in so many cases of which exposure to soap and water seems to play a major part.

Though Burtenshaw laid emphasis on fatty acids in skin self-sterilization, he nevertheless stated that the *p*H of the normal skin would alone be enough to kill many organisms. Eggerth (1926) found that the antibacterial action of soap was enhanced by an acid *p*H. The *p*H of the skin surface has been measured with indicators, by direct application of the electrodes of a *p*H meter, and by determining the *p*H of distilled water which has been left in contact with the skin. Though the results obtained by individual workers vary, there is complete agreement that the normal skin surface has an acid reaction—usually found to be between *p*H 5 and 6—and that certain regions are less acid, notably the flexural surfaces of the axillae and groins. This acid reaction may derive partly from sweat, since the *p*H of exocrine sweat is about 5.5 to 6 (Talbert, 1922). Furthermore, exocrine sweat may become more acid as it evaporates (Levin and Silvers, 1932), a change attributed by Bergeim and Cornbleet (1943) to increased concentration of lactic acid as the water disappears. These authors also found that if sweat is incubated without being allowed to evaporate its *p*H rises to 7 or more owing to the production of ammonia by bacteria. This may account for the relative alkalinity of the flexures, though, in addition, Marchionini (1929) found apocrine sweat to be nearer neutral or even slightly alkaline. Szakall (1955) decided, however, that the *p*H of the skin surface is due not to sweat but to amino-acids which are released or discarded in the formation of keratin, and the work of Dowling and Naylor (1960) points in the same direction.

There is no doubt that the use of soap on the skin leads to loss of its normal acidity. Bernstein and Herrmann (1942) found that the ordinary process of washing with toilet soap raises the *p*H of the skin surface by 1 to 1.5 units and that it takes about three and a half hours for the normal reaction to be restored. Martin-Scott and Ramsay (1956) found a greater rise in alkalinity after washing—up to *p*H 8—but a more rapid restoration to *p*H 5 in only 25 minutes. Evidently much will depend upon the thoroughness and the duration of

washing, the amount of soap used, and whether small amounts of soap remain on the skin from inadequate rinsing.

Effect of Prolonged Exposure

Klauder and Gross (1951) made particularly valuable observations on the effects of more prolonged exposure. They found that after ordinary washing the *p*H was restored to normal in three-quarters to two and a half hours. Longer periods of exposure while washing dishes raised the *p*H of the skin for four and a half hours; in canteen workers exposed several times during the day the recovery period was prolonged to 19 hours, so that in these subjects the hands were seldom at their normal *p*H. Each period of exposure to soap at *p*H 9.2 led to an increase of alkalinity of the skin from which recovery was so delayed that it was only on days off that the *p*H of the skin returned to normal.

The consequences of this are difficult to assess. The effect on the self-sterilizing power of the skin is doubtful. The *p*H of the skin is raised in eczema and in seborrhoeic dermatitis (Levin and Silvers, 1932), and Bernstein and Herrmann (1942) found that in eczematous patients the restoration of the *p*H to its former level after washing with soap takes longer than normal. This agrees with the findings of Burckhardt (1935) that the alkali-neutralizing time is longer than normal in eczematous subjects. The work of Anderson (1951) and of Beare *et al.* (1958) shows that this high *p*H is not restricted to the affected areas and that it persists after the eruption has cleared up. It is still not possible to say, however, whether the higher *p*H predisposes to eczematous eruptions, or to seborrhoeic dermatitis as Anderson suggested, or whether it is a consequence of these disorders. Many dermatologists believe that exposure to soap predisposes to dermatitis of the hands, but if this is so then several additional factors may be involved other than the mild elevation of *p*H which occurs with ordinary use of soap. There seems to be no clear evidence that maintaining the skin surface at a *p*H around neutral is in itself in any way harmful.

Soap and Skin Diseases

As to how often soap causes dermatitis there is great divergence of opinion. It is easy to believe that excessive use of soap may lead to degreasing of the corneous layer, to cracking, and hence to some degree of soreness—changes resembling chapping. Much greater difficulty arises in respect of frankly eczematous lesions with vesiculation or weeping. Klauder and Gross (1951) stated that 13% of their cases of industrial dermatitis were due to soap and water or to similar cleansers. Downing (1939) blamed soap and water as a contributing factor in nearly a quarter of his cases, and mentioned soap as the primary hazard in hotel and restaurant workers. Jordon *et al.* (1940) described a series of 239 cases of soap dermatitis in housewives, many of these taking the form of patchy vesicular eczemas involving the backs of the hands and one or several fingers. In the discussion which followed, their diagnosis was not questioned, and there appears to have been general agreement on the harmful properties of soap. But Gross (1941) regarded the cases of Jordon *et al.* as nummular eczema—which may indeed be expected to improve with rest and avoidance of soap, but the primary cause of which remains obscure.

In a general discussion on eczema of the hand Sulzberger and Baer (1948) consider primary irritants to be major influences, especially as predisposing or perpetuating factors, and they name soap as an outstanding cause. The part played by soap in individual cases is, however, extremely difficult to assess. Specific allergic sensitivity to soap is very uncommon, so that patch tests are of no value whatsoever in any given case. The behaviour of the eruption in relation to exposure to soap is seldom clear-cut, and patients' own statements upon which we may have chiefly to rely are often coloured by preconceived notions and by the opinions of their friends. To distinguish between a primary cause and an aggravating or perpetuating factor is usually impossible.

Jambor and Suskind (1955) carefully investigated 57 patients, of whom 35 were housewives, all having hand eczema attributed by the patients to the use of soap. On further investigation 30% of these cases were proved to be caused by other specific sensitivities.

The diagnosis of soap dermatitis often can be no more than surmise; eczemas of the hand have a high incidence in women in the fourth decade, and most women of that age are housewives, but we cannot necessarily assume that these two facts are causally related. The hands are a common site for eczema even in the absence of any identifiable external factor.

The experiments of Jambor (1955) and of Suskind (1957) are of particular interest. Jambor studied the effect of two kinds of soap, a neutral non-soap detergent, and an alkaline non-soap detergent, on 22 patients with hand eruptions which had been attributed to soap. One hand was immersed in 0.5% soap or detergent solution for half an hour daily and compared with the other, which was immersed in plain water. No difference between the hands or aggravation was seen in any case. As Jambor remarks, this may be because the solutions were not strong enough or because the exposure was not long enough or not frequent enough. Nevertheless, this strength of soap is that given by Fishbein (1945) for dish-washing (0.3 to 1%), and half an hour's immersion daily is indeed a considerable exposure. Suskind obtained the same entirely negative results in 45 subjects when the exposure was increased to half an hour twice daily.

One may recall that Brain (1956) has found that moderate use of soap does no harm to infants with eczema, for which, of course, it is the customary practice to forbid the use of soap. In my own wards I have used 5% toilet soap and 5% pure potassium palmitate as a cleanser in the treatment of eczema, seborrhoeic dermatitis, and psoriasis. The solution was rubbed on to the affected skin twice daily in order to remove applications such as Lassar's paste and zinc cream. The effect of these soap solutions was compared with that of applic. deterg. *N.F.* 1957 and liquid paraffin. Over a trial period of one month neither patients nor nurses nor doctors observed any irritant property in the soap solutions, except in contact with ulcerated surfaces. Their use was not continued because the other cleansers mentioned were found to be more efficient.

I do not wish to imply that soap plays no part in hand eczemas; but the observations I have just mentioned indicate a need for caution in arriving at general conclusions. The test of usage—the chief evidence upon which we can rely—is not easily arranged under properly controlled conditions. It is nowadays unusual to find a married woman who can completely avoid using soap, and the effect of rubber gloves is often, I think, clearly more harmful still. The occasional cases where hand eczemas have been ascribed to soap in paid employment,

where a change of occupation enables soap to be avoided, have not in my experience been at all impressive. Most of these eczemas have continued indefinitely and have thus given rise to the grave suspicion that the diagnosis of industrial (soap) dermatitis was wrong in the first place.

In the cases of Jordon *et al.*, mentioned above, the eruption was described as patchy, and I find it difficult to understand how total immersion of the hands in a liquid can produce well-outlined patches resembling nummular eczema with the adjacent skin completely normal. My own clinical observations lead me to believe that a truly eczematous soap dermatitis—that is, anything beyond the stage of fissuring and chapping—is uncommon and rarely severe. When it does occur the eczematous eruption, though perhaps patchy in degree, appears on a hand the whole skin of which shows some redness and chapping, a picture quite different from that of nummular eczema, which occurs in sharply outlined patches with completely normal skin between. Aggravation of eczema by soap is probably more common, though easily overrated; some burning and itching at the time of exposure followed by a degree of soreness is probably much more likely than any objective worsening directly caused by soap. In clinical practice we should be aware of the possibility of soap-aggravation, but the invariable and total prohibition of soap in eczema patients is often unjustified and inflicts an unnecessary hardship on the patient. These remarks are not intended to apply to ichthyotic subjects or to those middle-aged and elderly men in whom a dry eczematous eruption on the legs seems to be mainly due to washing.

Tests for Irritancy

It is well known that patch tests with soap solutions in normal people commonly give rise to positive results. It is probably equally well accepted that these are non-allergic primary irritant reactions. Lyon (1954) drew attention to the variability and uncertainty of these reactions, and this is discernible in comparisons of the various published series. Most of these reactions are mild, varying from a faint erythema to a slight degree of oedema and papulation. Nevertheless, even the mildest erythema from a soap patch test must surely indicate an irritant property, and it may be that the irritant property thus revealed is related to the irritancy of soap in ordinary use. Indeed, Kooyman and Snyder (1942) assessed the irritancy of soap by patch-testing and by user tests, and the results of the two methods were in close agreement. It seems likely, therefore, that the more convenient method of patch-testing probably gives a fair indication of the irritancy of a soap in actual use.

The irritancy of soap has been variously ascribed to alkalinity, to degreasing, to the essential irritancy of fatty acids, or to a combination of these factors. It has also been suggested that soap itself is not an irritant, or but rarely so, and that the irritancy usually observed results from the presence of free alkali, alkaline builders, resins, or other added substances.

Dr. Donoghue and I have carried out a series of experiments which were intended to throw some light on this problem (Bettley and Donoghue, 1960a). The effect of alkali alone in the *p*H range of soap solutions is negligible. My own experiments of patch tests with carbonate-bicarbonate buffer at *p*H 10 showed no primary irritancy. Other workers, such as Pillsbury and Shaffer (1939), have found the same, and patch tests with various soaps show no correlation between irritancy and alkalinity. The experiments of Blank (1939) indicate that the fatty acids of lower molecular weight, especially caprylic and capric, are primary irritants. In order to isolate the effect of these fatty acids of low molecular weight we compared the irritancy of potassium palmitate and verified Blank's view that the latter is much less irritant than an ordinary commercial soap. We found also that a soapless detergent, "teepol," is less irritant than soaps but becomes somewhat more irritant if its *p*H is brought up to 10. We suggest from these experiments that, though soap owes some of its irritancy to its fatty-acid content, and perhaps also to its degreasing effect on the skin, a further factor is present. We suggest that this factor is an increase in skin permeability which allows alkali and perhaps other irritants to reach the malpighian cells.

The living cells of the epidermis are normally protected from the outside by a barrier zone which is nearly waterproof and which resists penetration except by fat-soluble substances. Dr. Donoghue and I believe we have shown (Bettley and Donoghue, 1960b) that this barrier layer is attacked by soap in a way that makes it far more permeable to water and perhaps, therefore, to water-soluble irritants as well. We similarly examined a few other substances which may act as detergents or emulsifiers, and have gained the impression that their influence on the barrier zone is less or negligible.

These experiments seem to support the view that the irritancy of soap depends partly on its power of penetrating the epidermal barrier and reaching the cells of the malpighian layer, where fatty acids and probably alkali may exert their irritant properties. The irritant effect of free alkali, builders, resins, antiseptics, and other additives will presumably be much enhanced by, or even mainly dependent upon, the destruction of the epidermal barrier; thus the presence of soap may be a more important factor in producing irritation than these various additives which are often blamed.

Soap in Barrier Creams

Finally, I should mention briefly the use of soap in barrier creams. Soap is a common constituent of oil-resistant creams, being insoluble in most oils, and it is claimed to have a further advantage in helping to cleanse the skin at the end of work. In 1954 the Barrier Substances Subcommittee of the B.P.C. Revision Committee recommended certain type formulae. The composition of an oil-resistant barrier cream included 12% soap, and I think this is of doubtful wisdom. The Ministry of Labour (1946) pamphlet had already implied that a barrier cream should have a *p*H between 5.6 and 6.5. Yet the oil-resistant cream mentioned above gave a *p*H of 9.2 in 25% solution, and gave 25 positive reactions in 29 subjects patch-tested by Donoghue and me. Kooyman and Snyder (1942), as I have already mentioned, showed that the irritancy of patch tests goes hand in hand with the irritancy of soaps in a user test, so that we need not be too hesitant in drawing conclusions from patch tests. If, therefore, this barrier cream is applied often, and if it remains on the skin—as it is supposed to do—for several hours, then it is almost certain to be an irritant. The effect of soap in increasing the permeability of the epidermis, thus potentiating the effect of other irritants and sensitizers encountered during work, adds another grave disadvantage. Goldsmith and Hellier (1954) quote Tzank

et al. as believing that barrier creams may facilitate penetration of the skin by noxious substances.

From these considerations it follows that the use of soap-based barrier creams, so far from preventing industrial dermatitis, may substantially increase the risk The substitution of ethanolamine soaps may reduce alkalinity, but their effect in potentiating other industrial irritants remains problematical. Until more evidence is available it would certainly seem best to avoid any type of soap in a barrier cream.

Summary

Though soap has a considerable antiseptic activity, its action in washing bacteria off the skin surface is probably more important, particularly as regards recent contamination.

The power of the skin surface to sterilize itself may be impaired by washing with soap.

The normal acidity of the skin surface is changed towards alkaline by exposure to soap; the consequences of this are difficult to assess.

The irritant effect of soap on the skin tends to be overestimated. Such as it is, it depends upon primary irritancy of fatty acids and also upon the power which soap has to penetrate into the skin.

The inclusion of any soap in barrier creams is inadvisable.

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NEW STICK TEST FOR P.A.S. IN URINE

REPORT ON USE OF "PHENISTIX" AND PROBLEMS OF LONG-TERM CHEMOTHERAPY FOR TUBERCULOSIS

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Since para-aminosalicylic acid (P.A.S.) became generally available in the British Isles in the spring of 1948, streptomycin a year later, and the introduction of isoniazid in the treatment of tuberculosis in 1952, there has been an increasing weight of evidence of the value of effective long-term chemotherapy in the management of pulmonary tuberculosis.

The low toxicity in therapeutic dosage, ease and convenience of administration, together with potency, make P.A.S. and isoniazid the most satisfactory chemotherapeutic combination for tuberculous patients who have completed their hospital treatment and continue to have antibacterial drugs whilst living at home and working. Many such patients continue their ambulant combined therapy for two to three years.

Several methods have been described for determining the presence of P.A.S. in urine, depending on the colour produced with Ehrlich's reagent (Venkataraman *et al.*, 1948; Herold, 1951; Penman and Wraith, 1956; Ruiz, 1957), hypochlorite (Simpson, 1956), or ferric chloride (Simpson, 1956; Penman and Wraith, 1956; Dixon *et al.*, 1957). Though existing tests are reliable and sensitive when carefully applied in the laboratory or out-patient department, none have the simplicity of "clinistix" for glucose (Luntz, 1957) or "albustix" for proteinuria (Macgregor, 1958; Baron and Newman, 1958; Frazer, 1958).

In view of the comparable simplicity of "phenistix" reagent strips (primarily designed for the detection of phenylketonuria), and because it is based on the same principle as the ferric-chloride test, it was decided to examine in detail the suitability of this new test for the detection of P.A.S. in urine. With phenylpyruvic acid the reagent strip changes to a green colour (Rupe and Free, 1958; Baird, 1958; Nellhaus, 1959; Gibbs and Woolf, 1959), whereas with P.A.S. it turns a pink or purple, according to the amount present.

Material and Methods

Phenistix Test

This new test for P.A.S. in the urine employs impregnated paper sticks (phenistix reagent strips), which remain yellow when dipped in normal urine but become purple if the urine contains P.A.S. The test is based on the colour reaction which occurs with ferric ions and phenylpyruvic acid. Phenistix is impregnated with a mixture containing ferric and magnesium salts plus cyclohexyl sulphaminic acid.

Before embarking on clinical trials of phenistix in hospital wards, on chest clinic out-patients, and by patients themselves it was necessary to examine the sensitivity and specificity of phenistix in some detail.

The test was first compared with the two ferric-chloride tests—namely, that described by Simpson (1956) and the modified test used by Dixon *et al.* (1957).

Sensitivity of Phenistix in Comparison with Dixon's and Simpson's Ferric-chloride Tests

Known quantities of P.A.S. in a twofold range from 200 mg. per 100 ml. down to 0.8 mg. were added to nine specimens of normal urine and the three tests were applied to each specimen. Simpson's test (10% ferric chloride) is the most sensitive, giving a detectable colour change with as little as 1 mg. of P.A.S. per 100 ml. of urine. Dixon's test (3% ferric chloride) does not give a positive unless the concentration of P.A.S. in urine is at least 50 mg. per 100 ml. Phenistix gives a colour change with a P.A.S. content of about 12 mg. per 100 ml. Phenistix is thus slightly more sensitive than the Dixon test and slightly less sensitive than the Simpson test. A similar conclusion was reached by analysis of urines from patients taking P.A.S.

In all the subsequent studies phenistix was compared with Dixon's test, because this is the simplest test reported thus far.

Effect of a Single Dose of 5 g. P.A.S. (Sodium Salt) on Urinary P.A.S.

A single dose of 5 g. of P.A.S. (sodium salt) was given at 6 a.m. to 10 patients. Urines were collected two-hourly and tested by the Dixon and phenistix methods. Up to six hours all specimens were positive by both methods. From 12 hours onwards, negative results were obtained by the Dixon method. With phenistix all were still positive at 10 hours and all became negative by 18 hours.

Micro-analysis was undertaken in a urine giving a weak positive reaction to phenistix at 14 hours, and this specimen of urine contained about 25 mg. of P.A.S. per 100 ml. in the non-conjugated form. In another specimen which gave a weak positive phenistix reaction at 16 hours, analysis showed a P.A.S. content of 17 mg. per 100 ml.

Comparison of Sodium and Calcium B-P.A.S.

It has been suggested (Lauener and Friedrich, 1958) that calcium B-P.A.S. is not always detected by Dixon's method. This is not used as a routine in Birmingham, but its effect on phenistix was compared with the effect of the sodium salt. Four patients were given a single dose of 5 g. in cachet form, and four other patients received a single dose of 3.5 g. in powder form. As a control four patients were given a single dose of 5 g. of P.A.S. (sodium salt) in liquid form. Urine specimens were collected at two-hourly intervals for the next 16 hours and again at 24 hours. All specimens were tested by the Dixon test and by phenistix. The results showed no essential difference whether calcium B-P.A.S. or the sodium salt had been taken, though a positive colour with phenistix appeared a little earlier and lasted longer than with Dixon's test. It was found, however, that calcium B-P.A.S. could be detected in the urine for a slightly longer period than sodium P.A.S.

Specificity of Phenistix for P.A.S.

In addition to detecting phenylpyruvic acid (Rupe and Free, 1958; Nellhaus, 1959; Gibbs and Woolf, 1959) and P.A.S., phenistix reacts to the excretory products of other salicylates, including aspirin and phenothiazine compounds (Rupe and Free, 1958; Nellhaus, 1959).

Aspirin is probably consumed in larger quantities than any other therapeutic substance, as it is very widely marketed, prominently proclaimed, and popularized in periodicals, newspapers, and commercial television as an analgesic agent. Therefore a field study was organized, using phenistix for detecting substances other than P.A.S. in urine.

All new untreated patients referred to the Birmingham Chest Clinic for a consultant's opinion had a fresh specimen of urine collected, and these were tested with phenistix and the results recorded as "positive" or "negative" by the nursing staff. Patients with positive tests were asked what drugs, if any, they were taking.

A total of 1,370 consecutive new patients were examined in this way between May and October, 1959, and no patients on P.A.S. therapy were included in this study. The total number of patients with positive results was 91 (7%), and 69 of these were taking aspirin only and 17 were taking compounds containing aspirin. In five patients it was not possible to find out what drug had been taken. None of the patients with positive tests admitted taking drugs prescribed by their doctors which could be traced to chlorpromazine or related compounds. Therefore the effect of these drugs was not studied experimentally.

To study further the effects of salicylates on these urine tests a hospital trial was carried out. The effect of a single dose of 10 gr. (0.65 g.) of soluble aspirin was investigated in four patients. With the Dixon test a positive result was obtained in three out of four patients up to 10 hours after the aspirin had been taken. All were negative at 16 hours. With phenistix all four were positive up to 14 hours, and one remained positive for as long as 26 hours.

The effect of a fairly large dose of aspirin (40 gr. (2.6 g.) in one day) was also investigated on four patients. As might be expected positive results were obtained for a much longer time. At 24 hours three out of four were positive by the Dixon method and all four with phenistix.

Since in practice the percentage of patients taking aspirin is small, a positive phenistix result in a patient for whom P.A.S. has been prescribed indicates that he is likely to be taking his antituberculous drugs. A negative test is good evidence that a patient has not taken his P.A.S. for at least 12 hours.

Studies of Hospital Population, Using Phenistix

Previous studies have been confined to out-patients on long-term chemotherapy, and, though it is generally assumed that it is virtually impossible for hospital in-patients to omit taking prescribed drugs, we felt that this should be investigated nevertheless.

To assess whether P.A.S. was being taken as prescribed by hospital in-patients, repeated spot checks of the hospital population were made at unexpected times, using the phenistix urine test. At Romsley Hill Hospital complete population studies were done on three occasions, the first spot check being carried out on a Tuesday at 2 p.m., the second on a Sunday at 5 p.m. after visiting hours, and the third on a Friday at 8 a.m. At Yardley Green Hospital unexpected visits were paid to five tuberculous wards. Urine specimens were collected from all the patients on each occasion, and a total of 444 phenistix tests were carried out.

Of 444 tests on patients receiving P.A.S. in hospital, 436 (98%) gave a positive phenistix result and 8 (2%) a negative. Considering the results at the hospital where three successive checks were made, the first check showed one negative phenistix result in 105 patients. This one negative result was in a man aged 54 for whom

cachets had been prescribed. Four female patients (aged 16, 20, 28, and 59) gave a negative phenistix reaction in the second spot check, and one of these (the woman aged 59) also gave a negative result in the third spot check.

Results of Urine Tests with Phenistix on Chest Clinic Out-patients

Simpson (1956) examined the urines of 100 patients for whom P.A.S. had been prescribed, and found that 76 gave positive reactions with the hypochlorite test and the ferric-chloride test (10% solution). Thus 24% were "defaulters." Dixon *et al.* (1957) reported that 76 out of 151 patients (50%) on P.A.S. therapy were found, as a result of a simple urine test using 3% ferric chloride, to have defaulted in taking their prescribed P.A.S. Wynn-Williams and Arris (1958) followed a group of 153 out-patients and found that, despite special efforts to ensure the regular taking of drugs by their patients, 78 were "regular takers" and 75 (49%) "defaulters."

The object of this study was to check the frequency with which defaulters could be detected in a busy out-patient department, using the extremely simple phenistix test. A fresh specimen of urine was obtained from each patient attending the Birmingham Chest Clinic and the out-patient departments of Yardley Green and West Heath Hospitals for whom P.A.S. had been prescribed. Nursing staff were responsible for testing the urines of patients. This was usually done in the interval between the taking of the chest radiograph and the clinical examination, so that the test was completed and recorded as "positive" or "negative" before the patient was seen by the physician.

During a period of two months 705 tuberculous patients for whom P.A.S. had been prescribed were examined at the three out-patient centres in Birmingham. Of the 705 patients, 467 gave a positive phenistix result, and the remaining 238 (34%) were "defaulters." Table I

TABLE I.—*Result of Urine Test for P.A.S. by Phenistix in 705 Out-patients, According to Sex and Age*

Age Group (Years)	Male			Female		
	Total Tested	Negative		Total Tested	Negative	
		No.	%		No.	%
15–24	46	17	37	71	36	51
25–34	75	21	28	91	35	38
35–44	102	22	22	58	25	43
45–54	93	29	31	39	6	15
55–64	78	29	37	13	4	31
65+	26	10	38	13	4	31
Total ..	420	128	30	285	110	39

sets out the results of the urine tests for P.A.S. by phenistix, according to sex and age. Of 285 women, 110 (39%) gave negative results, a higher figure than the 128 (30%) of 420 men. The default rate was highest (51%) in young women aged 15–24.

The length of time that patients had been taking antituberculous drugs had a significant effect on the results, as can be seen from Table II. This is contrary to the findings of previous workers (Dixon *et al.*, 1957; Wynn-Williams and Arris, 1958), who did not find such a relationship in the small groups they studied. Where the duration of chemotherapy was less than one year, only 18% gave negative tests. The failure rate steadily increased with the length of time that patients had been receiving chemotherapy, and where drugs had been given for more than four years the default rate was 66%.

TABLE II.—*Results of Urine Tests for P.A.S. by Phenistix in Out-patients, According to Duration of Chemotherapy*

Months after Starting Chemotherapy	Total Tested	Negative	
		No.	%
1–12	204	36	18
13–24	281	103	37
25–36	131	52	40
37–48	68	33	49
Over 48	21	14	66
Total ..	705	238	34

TABLE III.—*Results of Urine Tests for P.A.S. by Phenistix in Out-patients, According to Length of Time Discharged from Hospital*

Months after Discharge from Hospital	Total Tested	Negative	
		No.	%
1–12	358	89	25
13–24	157	71	45
25–36	47	23	49
Over 36	18	8	44
Domiciliary chemotherapy with previous hospitalization ..	580	191	33
Domiciliary chemotherapy without previous hospitalization ..	125	47	38
Total	705	238	34

The correlation between the time elapsed since leaving hospital and the taking of P.A.S. as an out-patient was also significant. Of the 705 patients, 580 (82%) had begun their chemotherapy in hospital, and Table III shows the results of the urine tests for P.A.S. by phenistix related to months after discharge from hospital. Only 25% of the patients showed negative tests in the first year after discharge from hospital, but the percentage rose to 45 in the second year, and remained about this level thereafter.

The average for all 580 patients was 33% with negative tests, compared with 38% for the 125 patients who had received domiciliary chemotherapy only.

Of this group of 125 patients, 11% of 36 patients gave negative results during the first 12 months after starting antituberculous drugs; 39% of 36 in the second year; 45% of 31 in the third year; 65% of 17 in the fourth year; and 100% of 5 patients when the chemotherapy was continued more than four years.

Use of Phenistix by Patients

The object of this study was to see whether there was any advantage in the patient carrying out his own tests and so demonstrating the regularity or irregularity of his drug-taking habits. Self-testing could be of value only as long as the patient did not associate his chemotherapy-taking with the result of his urine tests.

Twenty patients chosen as likely to be co-operative were each given a bottle containing 50 phenistix and asked to test their own urines last thing at night for 50 days. None of them knew that the test was for P.A.S., and some of them believed that a drive for the detection of diabetes was being made. They were shown typical positive and negative colours, and it was made clear to them that they could expect either positive or negative results, which were recorded on a sheet each night as "purple," "no change," or "test not done." The results of the patients' self-testing with phenistix are shown in Table IV. None of the patients had any difficulty in carrying out the tests, and the results revealed some significant and salient sidelights on patients'

TABLE IV.—*Results of Phenistix Self-testing in 20 Patients over 50 Days, with Reasons Given for Negative Tests*

Patient	Form of P.A.S.	Phenistix Tests			Remarks
		Pos.	Neg.	Not Done	
1	Cachets	46	4	0	P.A.S. taken late at night after urine test on four occasions, so that there was more than 12 hours between doses
2	,,	48	0	2	
3	,,	30	20	0	P.A.S. not taken during week-ends and for a week
4	,,	42	8	0	P.A.S. not taken on 7 Sundays and insufficient P.A.S. on one day
5	,,	48	2	0	Did not take P.A.S. on one day with negative result. Therefore repeated this "experiment" on another day and discovered the relationship
6	,,	50	0	0	
7	Tablets	48	0	2	
8	Cachets	50	0	0	
9	Granules	46	0	4	
10	Liquid	43	7	0	Insufficient P.A.S. for a week over Whitsun
11	Tablets	50	0	0	
12	,,	0	50	0	Frank confession to not taking drugs since discharge from hospital
13	Cachets	50	0	0	
14	Granules	50	0	0	
15	Liquid	47	3	0	Missed taking P.A.S. for 3 days through insufficient medicine
16	Cachets	50	0	0	
17	,,	36	8	6	Forgot to take his drugs on 8 days and had 6 very late nights, on which occasions he did not do the tests
18	Granules	49	0	1	
19	,,	50	0	0	
20	Cachets	50	0	0	
	Total ..	883	102	15	

drug-taking habits. One patient always omitted his drugs during week-ends, and another had a rest day on Sundays. Three patients failed to take their drugs for one, three, and seven days through not having a sufficient supply.

Twelve patients had taken their chemotherapy regularly throughout the test period, and only one patient had taken no drugs at all. This patient had given no indication that he was a defaulter at his routine examinations at the follow-up clinic prior to the start of urine-testing. The other seven patients gave negative tests on 2, 3, 4, 7, 8, 8, and 20 occasions respectively during the 50-day test period. The reasons are explained in Table IV. In four patients the negative tests occurred sporadically as isolated incidents, and in three they occurred as runs.

Discussion

The most practical way of checking whether a tuberculous patient is taking his P.A.S. regularly is to test the urine. The advantages of phenistix over the conventional tests for P.A.S. in urine are many. The new test does not require any laboratory equipment or stock solutions which may be caustic and staining. The test is quickly carried out by either physician or nurse and is extremely simple and sensitive: it consists in merely dipping the impregnated end of the paper stick into the urine. The presence of P.A.S. causes a change of colour from yellow to purple, the depth of which depends upon the concentration of P.A.S. No attempt was made to relate the depth of the colour reaction with the P.A.S. content of the urine, though it was noted that the depth of colour varied from time to time.

A negative urine test is evidence that no appreciable amount of P.A.S. is present in the urine and that no P.A.S. has been taken for a number of hours (Simpson, 1956; Dixon *et al.*, 1957; Wynn-Williams and Arris, 1958; Fox, 1958). The exact number of hours depends principally on the sensitivity of the test employed. With the Dixon test a negative result indicates that no P.A.S. has been taken for 10 to 12 hours, whilst a negative phenistix test indicates that no P.A.S. has been taken for 12 to 18 hours.

Like the ferric-chloride tests, phenistix gave positive results to aspirin. Though 7% of a group of unselected patients were taking aspirin prior to having their urine tested, we do not feel that this invalidates the use of phenistix in view of the importance of detecting patients who are not taking P.A.S. It must be remembered that the interference of salicylates is important only in those patients who are omitting their P.A.S., as the physician may be misled by a "false" positive. Only a small proportion of the patients failing to take their P.A.S. regularly are likely to be taking aspirin at any given time.

It is of interest that unexpected checks on hospital in-patients having continuous chemotherapy revealed that 8 (2%) of 444 tuberculous patients had omitted to take their P.A.S. This is frequent enough to draw attention to the fact that not all patients can be relied on to take their medicines even in hospital unless the nurse makes sure that the liquid, tablets, cachets, granules, or powders are actually swallowed by the patient. In these cases it was ascertained that the nurses had not waited to watch their patients swallow the cachets as they invariably do with liquid P.A.S. given in a medicine glass.

The use of phenistix for the estimation of urinary P.A.S. in 705 out-patients furnished further satisfactory evidence of its usefulness. One-third of the patients gave negative results and there was a slight difference between the sexes, 30% of the men and 39% of the women giving negative results. Similar sex difference has been reported in Indian out-patients (Tuberculosis Chemotherapy Centre, Madras, 1959), more irregularity in self-administration being found among female than among male patients.

The fundamental problem of continued drug therapy in the treatment of any chronic disease is the regularity with which patients will administer the prescribed preparations to themselves, whether it be for months or years. This was discussed by Fox (1958) with particular reference to pulmonary tuberculosis.

The Tuberculosis Society of Scotland (1958) has been carrying out a controlled trial of patients with tuberculous lesions of doubtful activity picked up on mass radiography. One group was kept under observation only, and the other was given chemotherapy with P.A.S. and isoniazid for a minimum of six months. Over a two-year follow-up period there was a breakdown rate of approximately 17% in those undergoing observation only, compared with 8% in the group receiving treatment. All the definite breakdowns in the so-called treated group were in patients who had failed to take their chemotherapy as advised. This finding emphasizes the great difficulty in ensuring that all patients on out-patient treatment take their chemotherapy as directed.

The diseases requiring self-administration of drugs by patients for long periods may be considered under two broad headings. Firstly, there are disorders where the patient is reminded that he must take his drugs regularly by the fact that omitting them can cause unpleasant symptoms in a short time. Examples are the long-term treatment of coronary thrombosis with anticoagulants, of epilepsy with anticonvulsants, of peptic ulceration

with antacids, of auricular fibrillation with digitalis, and of rheumatoid arthritis with corticosteroids. Secondly, there are conditions where the effects of omitting the drugs are often not apparent to the patient for some considerable time. In these cases there is a greater likelihood for irregularity in the taking of drugs. Pulmonary tuberculosis under long-term chemotherapy and rheumatic fever treated prophylactically fall into this category and are considered below.

In addition to the examples quoted by Fox (1958), there are other conditions for which patients cannot be depended upon entirely to take their medicine as prescribed regularly. For example, not all patients with a hypochromic anaemia take their iron preparation by mouth consistently (Hawkins *et al.*, 1950), while failure to keep to a gluten-free diet was the commonest cause of relapse in idiopathic steatorrhoea (French *et al.*, 1957). In the oral treatment of pernicious anaemia, Wilkinson (1949) found that 15 out of 441 patients who neglected to continue with their treatment relapsed. Irregular and inconsistent treatment has also been reported in diabetes (Cosnett, 1959; Campbell and McNeill, 1959).

A close parallel may be drawn between regular prophylaxis in rheumatic fever and continuous antituberculous therapy in pulmonary tuberculosis. The Rheumatic Fever Committee of the Royal College of Physicians (1957) recommended that the prophylactic regime for the rheumatic child should consist in taking chemotherapy for at least five years. A W.H.O. Expert Committee on Rheumatic Diseases (1957) stated that it was unlikely that prophylaxis could be continued successfully if the physicians did not accept and assume continuous responsibility.

Similarly in pulmonary tuberculosis, we feel that one of the most important causes of failure to take prescribed drugs is the lack of continuity of supervision by one experienced physician. The value of this supervision was very apparent in pre-chemotherapy days when the best results in therapeutic pneumothorax were obtained where the induction, refills, and supervision were all carried out by one doctor. At the present time if the physician in charge is prepared to take immense trouble to impress on his patients regularity in taking drugs as well as the consequences of neglecting treatment, the patient is much more likely to take his chemotherapy conscientiously.

Tactful questioning of some of the patients with a negative phenistix test indicated that there are many reasons for irregularity in taking P.A.S. by patients on domiciliary treatment.

1. P.A.S. has the disadvantage of being somewhat bulky and unpleasant to take and may act as a gastro-intestinal irritant, so that with long-continued use most patients experience transient disturbances in the alimentary tract. Patients who suffer anorexia, nausea, vomiting, abdominal discomfort, or diarrhoea often have to discontinue the drug for one or more days at a time, thereby accounting for a proportion of those who give a negative phenistix test on any given day. One patient instituted his own system of a relief period by omitting the drugs every Sunday, and another omitted his drugs over week-ends (Table IV).

2. Simple forgetfulness plays a part in some patients. The patient with quiescent disease feels well generally, leads a fairly normal life while working, and on occasion forgets to take his drugs, particularly when away from home or out late at night.

3. Patients sometimes run out of their supply of medicine. This was found in 3 of the 20 patients who tested their own urine with phenistix for 50 days (Table IV).

4. The urine may stain underclothing or bed-linen, and make the P.A.S. unpopular with some patients. This objection to P.A.S. is not encountered often, because of reticence on the part of patients.

5. After a long period on chemotherapy there is a tendency for the patient to be less regular with his drugs or to discontinue them altogether, except in obsessional patients. There was a distinct correlation between the length of time that patients had been having drugs and the default rate: the longer they had been taking the drugs the less reliable they became (Table II). A similar correlation was found with the length of time that patients had been discharged from hospital (Table III). The quiescent patient is tempted to think that he is cured, sees no need for medication, and therefore stops taking his drugs. The problem to be settled is for how long antituberculous drugs need be given if patients are to recover fully without risk of relapse in the years following. Follow-up studies of patients treated with prolonged chemotherapy have not extended long enough for an answer to be made to this problem yet.

6. A small number of patients are uncooperative, and no amount of exhortation on the part of the physician will make them any less quixotic in their demeanour.

If long-term antituberculous chemotherapy is to succeed for the vast majority of patients, with failure to take drugs confined to the small hard core of uncooperative patients, then the problem demands attention to the following points. The chest physician must accept and assume continuous responsibility for his tuberculous patients, and every effort must be made to emphasize in the strongest possible terms, with persuasive propaganda and compelling conviction, the importance of taking the drugs as prescribed. In these circumstances it is to be hoped that the default rate would be much less than that found in the present study. There was some excuse for omitting urine-testing when only the cumbersome laboratory methods were available, but there is no excuse now that a test as simple and rapid as phenistix is obtainable.

The increasing tendency to allow tuberculous patients home at an early stage of treatment in order to continue chemotherapy as out-patients needs to be reconsidered in the light of these findings. It is inadvisable to permit young adults aged 15–24 of either sex, females of 25–44, and males over the age of 55 to leave hospital after only a short stay, as patients in these age groups showed the highest default rates. Hospital treatment for a much longer time would be far more appropriate for such tuberculous patients.

Summary

A new test for P.A.S. in urine ("phenistix" reagent strips) is described. Phenistix has a good degree of specificity for P.A.S., and no essential difference was noted whether the sodium or the calcium salt of P.A.S. had been taken. Positive results for reasons other than P.A.S. were relatively few; 1,370 consecutive new out-patients were examined and positive results with phenistix were obtained in 91 (7%), the majority due to aspirin.

The extreme simplicity of phenistix, together with its optimum sensitivity, makes it the ideal test for the qualitative estimation of P.A.S. in urine in both out-

patients and in-patients. A negative phenistix test is evidence that no appreciable amount of P.A.S. is present in the urine and that no P.A.S. has been taken for 12 to 18 hours.

Of a total of 444 tests at unexpected times on hospital in-patients receiving P.A.S., 436 (98%) gave a positive and 8 (2%) a negative result. Not all patients in hospital can be relied on to take their medicine unless the nurse makes sure that the medicine is actually swallowed.

Of 705 tuberculous out-patients on P.A.S. therapy, 467 gave a positive phenistix result, and the remaining 238 (34%) were "defaulters." Negative results were found in 39% of the women and 30% of the men. The length of time that patients had been taking chemotherapy and the time elapsing since discharge from hospital had a significant effect on the results. The failure rate steadily increased in both instances with each year of the duration of chemotherapy. It is inadvisable to permit young adults aged 15–24 of either sex, females aged 25–44, and males over the age of 55 to leave hospital after only a short stay, as patients in these age-groups showed the highest default rates.

Self-testing by 20 patients revealed the reasons for negative tests and gave insight into patients' drug-taking habits. The problem of self-administration of drugs is discussed. It is suggested that the best results will be obtained in cases where the whole course of treatment is directed by one experienced physician and that continuity of medical surveillance is essential.

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USE OF A VACUUM EXTRACTOR (VENTOUSE) IN OBSTETRICS

BY

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For at least 250 years attempts have been made to shorten labour by means of traction applied to the foetal head. Early in the seventeenth century the obstetric forceps was invented by the Chamberlin family, and modifications of it are in use throughout the world to-day. As an alternative, the use of a vacuum to affix a tractor to the foetal scalp has been attempted since Yonge used a cupping glass in 1706. The next attempt of the kind appears to have been that of Simpson, in 1849, who described a rubber cap attached to a brass syringe. In 1890 MacCahey used a rubber cap with a solid handle which was pressed on to the presenting part and created its own vacuum.

Torpin (1938) reported the delivery of 10 women with prolonged second stage by means of a rubber suction cup extracted by a vacuum pump, and bearing a loop for traction and lugs which enabled the operator to aid rotation. In 1947 Couzigou described the use of a metal cup, which he called the "ventouse," the name now in general use in the French-speaking countries. Koller (1950) applied prolonged weight traction to the foetal head in cases of uterine atony by means of a suction cup, and with a weight of 0.5–1.5 kg. for up to 18 hours achieved augmentation of the uterine contractions and acceleration of the labour. An apparently unique use of the vacuum principle was that of Gastaldo (1951), who occluded the lower birth canal with a metal cup covered with rubber. Subsequent creation of a vacuum was said to promote advance of the foetus down the birth canal. Finderle (1952) described his trumpet-shaped metal cup extracted by a vacuum pump, and in 1955 he reported that the instrument had replaced forceps completely for three years and that in 132 deliveries no deaths or complications were attributable to the extractor.

Malmström (1954) described his instrument, which was used primarily to increase labour pains in inertia by promoting good contact between scalp and cervix and so leading to increased stimulation of the uterus. Prolonged weight traction for up to several hours was originally used, but, later, direct extraction or improvement of the position of the head for subsequent forceps delivery was undertaken. Later, Malmström (1957a) described the modification of his instrument which is now the form most widely used. Since his first report his instrument has been used in many European countries, including Russia (Petchenko, 1958), North and Central Africa, China, and South America. We have been unable to find any report of its use in either the British or the North American literature, though at the Second World Congress of Obstetricians and Gynaecologists in Montreal in 1958 films demonstrating its use were shown by Muller, of Strasbourg, and deWatteville, of Geneva.

The only British references we have found are in nursing publications. Lobban (1955) claims that

mothers preferred this instrument to forceps, but observed that "it seems likely to receive a more conservative reception in Britain than elsewhere." Malmström (1957b) described his method at the Stockholm Congress of Midwives, and a report of his paper was subsequently published in England. Though the Malmström instrument was used initially for the application of prolonged traction in uterine inertia (Malmström, 1954; Aschan and Saloheimo, 1955), more recently this or similar instruments have been used increasingly for direct extraction and delivery. In many clinics it has largely replaced forceps (Blackman, Pierret, and Dussart, 1956; Sohie, 1957; Rosa and Piraux, 1957; Snoeck, personal communication, 1958; Bruniquel and Israël, 1958; Goldberg and Levy, 1958), but several authors think it should be used as a supplementary aid rather than as a substitute for forceps (Meinrenken and Schieferstein, 1957; Pigeaud, 1957; Dexeus, 1957).

The Ventouse

The instrument we have used is the modified Malmström vacuum extractor which has three metal cups, 20 mm. deep and 40, 50, and 60 mm. in diameter (Fig. 1). From a plate within the apex of each cup a chain passes inside a flexible rubber tube to a traction bar and is there secured by a pin. The rubber tube fits on to a metal tube traversing the traction bar, and from this a further rubber tube leads on to a vacuum bottle fitted with a screw-release valve. The bottle carries a manometer graduated up to 1 kg./cm.² and is exhausted by means of a vacuum pump. On the two larger cups is a small knob which can be used either to promote rotation or merely as an indicator of the position of the cup.

Application.—The largest possible cup is inserted in much the same way as a ring pessary into the birth canal and applied to the presenting part, the perineum being pressed back either with the cup or with the fingers of the other hand. With a cephalic presentation the cup should be applied as far back as possible on the head in order to promote flexion, and care must be taken that the membranes are ruptured and that neither vaginal nor cervical tissue is interposed between the scalp and the cup. An artificial caput is now raised on the presenting part by the production of a vacuum within the cup of up to 0.8 kg./cm.² This must be achieved by a gradual reduction of pressure, and 6 to 10 minutes are usually necessary to ensure complete filling of the cup by the scalp and therefore adequate adhesion. Traction is then applied in the axis of the pelvis by pulling on the traction bar with the right hand, two fingers of the left hand being used to displace the perineum, to control adhesion of the cup, and if necessary to push the head towards the hollow of the sacrum or to promote flexion. Traction should usually coincide with pains, and delivery is completed in the usual way with or without episiotomy as required. Reduction of pressure by opening the screw valve permits detachment of the cup from the foetal scalp.

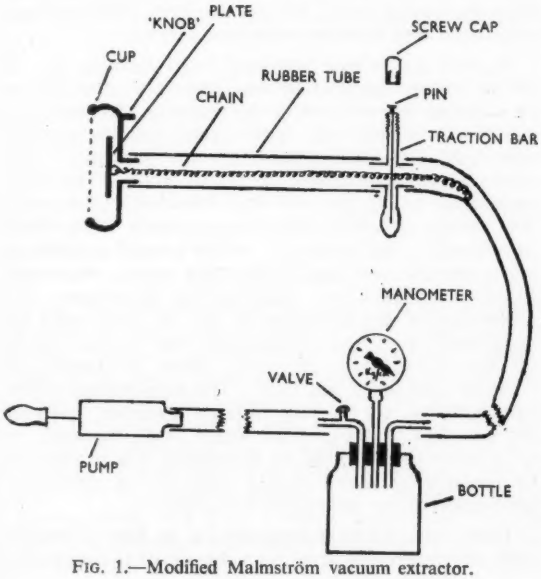

FIG. 1.—Modified Malmström vacuum extractor.

Anaesthesia.—In many cases no anaesthesia is required (Blackman *et al.*, 1956; Dexeus, 1957; Bruniquel and Israël, 1958; Goldberg and Levy, 1958), but most authors have used either local perineal infiltration or pudendal block (Malmström, 1954; Sohie, 1957; Pigeaud, 1957), Goldberg and Levy (1958) have referred to the advantage of the avoidance of general anaesthesia which the instrument permits in cases of respiratory or cardiac disease. Eschbach and Gandar (1957) observe that it is not only less dangerous but also less painful than forceps.

Effects on the Mother

There is widespread unanimity about the extreme safety of the method for the mother. As there is no instrumentation high in the birth canal, the risks of introduction of sepsis are minimized (Sterckx, 1957). No part of the instrument encroaches on the narrow diameters of the birth canal, and so all the available space in the pelvis remains for the passage of the foetus. Excessive or ill-directed efforts will result in detachment of the ventouse, and consequently damage to the birth canal is avoided (Goldberg and Levy, 1958). Laceration of the perineum is minimal and episiotomy can be undertaken if required. Though Voegeli (1958) described a third-degree tear in his series he attributed this to the use of undue force. No bladder complications have been recorded in the literature, though in one of our cases early urinary retention occurred, with slight haematuria for one day after an easy assisted delivery.

Effects on the Foetus

The presence of a large artificial caput is inevitable in the very nature of the method, and at first this presents a formidable swelling aptly described by Rosa (1955) as a "chignon." It rapidly diminishes in size and has almost completely abated in a few hours (Fauvet and Scheele, 1956), when it is usually no more obvious than a normal caput succedaneum (Fig. 2). Small ecchymoses or tiny ulcers around the perimeter of the cup may persist for a day or two, but these usually heal without causing any trouble. Slight scalp necrosis which cleared up satisfactorily was described after prolonged weight traction in one of Malmström's (1954) cases, and, in Vienna, Antoine (1959) abandoned this particular use of the instrument because of this complication. Roloff (1959) states that the instrument should not remain *in situ* for longer than 40 minutes in view of the risks of necrosis of the scalp. Goldberg and Levy (1958) state that the only possible foetal complication is the formation of a cephalhaematoma, which was avoided in their

series of 70 cases by the administration of vitamin K_1 and the application of a pressure-dressing on the foetal scalp. Muller (1959) states that even these measures are now regarded as unnecessary. Blackman *et al.* (1956) found cephalhaematoma in 10% of their cases but stated that there was no permanent scalp damage.

The only authors reporting a high incidence of injury are Meinrenken and Schieferstein (1957) with 29.6% and Chang (1958), using a Finderle instrument, with 31%, none of which in either series was serious. Pigeaud (1957) stated that in 200 cases mother and child escaped

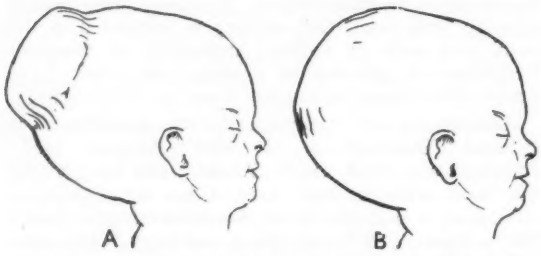

FIG. 2.—Head of child (A) immediately after delivery showing "chignon," and (B) 10 minutes later, when appearance is similar to normal caput succedaneum.

injury when the pressure was limited to 0.7 kg./cm². The great majority of authors are agreed on the lack of trauma to the foetus (Koller, 1950; Malmström, 1954; Finderle, 1955; Fauvet and Scheele, 1956; Blackman *et al.*, 1956; Sohie, 1957; Sterckx, 1957; Dexeus, 1957; Bruniquel and Israël, 1958; Goldberg and Levy, 1958; Berggren, 1958), and Rosa (1955) has calculated mathematically that compression of the foetal head by this method is less than one-twentieth of that applied in forceps deliveries.

Personal Experience

We first became interested in this instrument when one of us (J. A. C.) visited Snoeck's clinic in Brussels in 1957 and found that forceps had been displaced completely for a period of three years. Snoeck was extremely enthusiastic about the advantages of the instrument, and it was decided to try it here. In the 14 months since May, 1958, the ventouse has been employed in 100 women—79 were primigravidae, and 13 had had one, 6 had had two, and 2 had had three previous children.

During the 12 months up to April, 1958, forceps were applied in 10.3% of 936 deliveries. During the next 12 months the forceps rate fell to 4.1% and the vacuum extractor was used in 6.6% of 1,035 deliveries. In 88 cases delivery was successfully completed with the ventouse alone. In 12 instances, when an extraction had been started with the ventouse, forceps were employed to complete the operation. In eight of these (the cervix was incompletely dilated in four) dilatation of the cervix and rotation and descent of the head were obtained with the aid of the ventouse before the application of forceps, as described by Malmström (1954). In a few cases with acute foetal distress, if the ventouse was not immediately effective, forceps were used so as to secure delivery more rapidly. Three of the comparative failures of the ventouse were early cases, and we believe that inexperience of the new method contributed to the need to use forceps to complete delivery. The other cause of failure of the method was relative disproportion, where the powerful traction necessary to secure delivery could be applied with forceps but led inevitably to detachment of the ventouse.

All the children, whose weight ranged from 4 lb. 8 oz. to 11 lb. 2 oz. (2,040 to 5,045 g.) were born alive, with the exception of two in whom intrauterine death had preceded delivery by four hours and five days respectively. There were two neonatal deaths, in one of which forceps delivery was undertaken for acute foetal distress in a case in which difficulty had been experienced in obtaining adhesion with the ventouse. The second was a first twin weighing 4 lb. 8 oz. (2,040 g.) who died from tentorial tears six hours after an easy delivery. All the remaining infants made good progress and left hospital in good condition. In all cases the "chignon" resolved rapidly and had abated materially within six hours of delivery. In two cases small abrasions around the periphery of the caput persisted for about a week, but these healed without complication. No pressure-dressing or other similar treatment of the scalp has been found necessary.

Adhesion of the instrument was satisfactory in all but 10 cases. In seven of these completion of the delivery was undertaken with forceps as described above; in the other three repeated reapplication of the instrument enabled delivery to be completed. Most patients were delivered in the lithotomy position, but in four the dorsal and in two the left lateral position was used. Each was quite satisfactory. The longest time spent over delivery was 60 minutes and the shortest 7 minutes, the average being about 20 minutes.

In 84 cases the cervix was fully dilated, but in 16, including 13 primigravidae, dilatation was incomplete. In the latter group the indications for interference were: long labour with inertia in nine, foetal distress in six, and uterine scar in one.

In Case 87, a gravida-4, foetal distress occurred when the cervix was sacral, not completely effaced, and dilated only two fingerbreadths. Ventouse extraction under general anaesthesia, with incision of the cervix, secured in 45 minutes delivery of a child in satisfactory condition, successively larger cups being applied. The delivery was complicated by a post-partum haemorrhage from the incised cervix, but this was controlled by suture and there were no other complications.

General anaesthesia was used in 10 cases, in five of which forceps application was necessary after failure to complete extraction with the ventouse. In two cases breech extraction was undertaken, and in another extremely exhausted patient it was felt that local anaesthesia would impose an undue strain. The ninth patient, an Italian girl with little knowledge of English, was wildly excited and unmanageable with local anaesthesia. The last case in which general anaesthesia was necessary was Case 87, described above. Pudendal-block anaesthesia was employed in 50 patients and infiltration of the perineum in 36. In four cases no anaesthesia was used. Episiotomy was carried out in all but eight cases. In many cases gas-and-air or "trilene" analgesia was used. The employment of the ventouse did not in any instance increase maternal distress, and in those cases where local, regional, or no anaesthesia was used no discomfort was occasioned to the mother which caused difficulty in either the application or the subsequent extraction.

There were six twin pregnancies, in four of which both twins were extracted with the aid of the ventouse.

In the fifth the second twin, presenting by the breech, was delivered manually, and in the sixth the first twin was delivered with the aid of the ventouse applied to the breech, and the second by application to the vertex, the head being above the pelvic brim.

In 100 instances the vertex presented, the occiput being anterior in 57, lateral in 26, and posterior in 17 when delivery was begun. In the posterior positions face-to-pubis delivery occurred in 10 and "auto-rotation" (Evelbauer, 1956) in 7. In the 26 lateral positions of the occiput rotation occurred in 24; one child, weighing 5 lb. 9 oz. (2,525 g.), emerged with the occiput more or less lateral, and in another Kielland's forceps rotation proved to be necessary. Two brow presentations were encountered. One was a second twin weighing 5 lb. 6 oz. (2,440 g.) who was delivered as a brow from a large pelvis. The second brow presentation was flexed automatically by means of the posterior cephalic application of the instrument, and was delivered as an occipito-posterior, auto-rotation through 140 degrees having occurred. Three cases presented as frank breeches with delay in the second stage. Application of the ventouse to the anterior buttock secured descent from high to low pelvis, so that an easy extraction could be carried out. Kaeser (personal communication, 1958) and Bruniquel and Israël (1958) report a similar use of the ventouse in breech delivery.

The accompanying Table shows the principal indication for intervention in each case. Uterine intertia was the predominant factor in cases with a long first stage, the longest of which lasted 51 hours. In five of these cases intervention was undertaken as soon as possible in the second stage, but in nine the ventouse was applied before the cervix was fully dilated.

Indications for Intervention

Indications	Primi-gravidae	Multi-parae	Total
Long or complicated first stage	12	2	14
Foetal distress	16	7	23
Unprogressive or prolonged second stage	34	10	44
Other maternal factors*	17	2	19
	79	21	100

* Severe toxaemia in 10, cardiac disease in 3, hysteria in 3, uterine scar after extensive myomectomy in 1, diminished respiratory reserve after lobectomy in 1, and laparotomy for acute appendicitis six hours before delivery in one.

Foetal distress was the leading indication in 23 cases, in six of which the cervix was incompletely dilated. Both neonatal deaths were included in this group. Prolongation of the second stage occurred in 44 cases. In most of these the cervix had been fully dilated for more than two hours; in the others there was obvious failure to progress or some additional feature was present.

Discussion

Our first introduction to this instrument came from a French-speaking source, and for this reason and for brevity we have used the term "ventouse" in our text and in our work rather than "vacuum extractor," the name employed by Malmström. Our personal experience and our study of the literature have indicated certain advantages of this instrument as compared with forceps. The method is of extreme simplicity, and in this unit has become popular with the medical and nursing staff, and even house-surgeons quite new to operative obstetrics have had no difficulty in picking up the technique. The only notable feature of the technique requiring discussion is the occasional difficulty in securing adhesion. Our own experience is that failure of adhesion has become rare when attention has been paid to the following points. Firstly, plenty of time must be allowed for the reduction of pressure, and this must be done by stages over a period of 6 to 10 minutes. Secondly, traction must be perpendicular to the transverse axis of the cup. When the foetal head lies at a relatively high level in the pelvis the cup of the ventouse must be placed on the most posterior part of the head that can be reached in order to achieve this perpendicular traction. This means that it is not always advantageous to place the cup on a preformed caput (cf. Malmström, 1957a).

We cannot confirm the view of Charrier and Docquier (1957) and Cunningham (1958) that failure of the method may be due to omission to rotate the head before application of the ventouse. In our series we have found that the ventouse can promote flexion of the head and can achieve rotation by means of those natural forces promoting rotation which forceps tend to inhibit. These features make the instrument particularly useful in cases of malpresentation and malposition such as deep transverse arrest. This use of the ventouse offers several advantages over either manual or forceps rotation, particularly in reducing the need for general anaesthesia and also in avoiding the necessity of displacing the head upwards in the pelvis.

We have used the ventouse to replace forceps and not, as has Pigeaud (1957), to shorten labour in normal primigravidae. Rosa (1955), Sterckx (1957), and Goldberg and Levy (1958) all refer to their readiness to apply it in the same way as "forceps de complaisance" because of its great safety.

One of the great advantages of this instrument over forceps is that it can be applied in the first stage of labour to promote dilatation of the cervix. This is achieved in a physiological manner by augmenting uterine contractions as well as by drawing the presenting part down the birth canal, usually without tearing or incision. The smallest cup can be applied at about half dilatation of the cervix, but as dilatation proceeds a larger cup may be substituted and more powerful traction employed.

Traction may be either continuous by means of a weight as described by Koller (1950) and Malmström (1954) or by hand simultaneous with uterine contractions. In the latter method, which we have used exclusively, the active co-operation of the mother is an important advantage (Blackman *et al.*, 1956). The instrument has been applied to the head at all levels in the pelvis, though Bourg (1957) and Sohie (1957) both regard non-engagement of the head as a contra-indication. In our own series, in two second twins the head was at the pelvic brim at the time of application and no difficulty with the deliveries was experienced. Sohie (1957) also refers to this use of the ventouse to avoid internal version and breech extraction for delayed second twins. In all our remaining cases the presenting part was in the pelvic cavity. Cephalopelvic disproportion is usually regarded as a contraindication to the use of the ventouse (Finderle, 1955; Aschan and Saloheimo, 1955; Blackman *et al.*, 1956), and we have found that forceps delivery is required when more than a minor degree of disproportion is present. Bruniquel and Israël (1958), however, have advocated its use as a "trial tractor" in cases of possible disproportion in much the same way as the "trial forceps" of Jeffcoate (1953),

and Muller (1959) stresses the greater safety of the ventouse as compared with the forceps in this connexion.

In this unit we have used the instrument to terminate labour for delay in the second stage, for maternal and foetal distress, and in a variety of special cases. Special indications referred to in the literature, apart from those that we have encountered in our own series, include eclampsia and "shock" (Finderle, 1952), epilepsy (Goldberg and Levy, 1958), weakness of the abdominal wall (Bruniquel and Israël, 1958), marginal placenta praevia (Sterckx, 1957; Meinrenken and Schieferstein, 1957), premature separation of the placenta (Finderle, 1955), prolapse of the cord (Meinrenken and Schieferstein, 1957), and rigidity of soft tissues (Maire, (1957).

With regard to the use of the instrument for premature births, we have delivered nine babies weighing less than 5 lb. 8 oz. (2,485 g.) and in eight of these have been satisfied that the ventouse did not cause injury. All these babies made good progress after delivery, with the exception of Case 30, in which the child, weighing 4 lb. 8 oz. (2,040 g.), died from tentorial tears. This damage may have been caused by the instrument, but a similar risk of intracranial haemorrhage is, of course, present in forceps delivery or even in spontaneous delivery in children of this size. Both deWatteville (1958) and Voegeli (1958) have reservations regarding the use of the ventouse for delivery of premature babies. The latter refers to the ability of the forceps blades to protect the premature head from soft-tissue damage, though Rosa (1955) regards this as completely illusory. We cannot, therefore, at this stage say for certain whether ventouse extraction of the smallest premature babies is to be recommended.

In breech deliveries, when progress has ceased with the buttocks low in the pelvis, application of the ventouse may avoid the necessity to bring down a leg under a general anaesthetic.

There are certain instances where the ventouse cannot replace forceps; these include face presentation, the aftercoming head, and transverse lie. After manipulation of an oblique or transverse lie to a cephalic presentation there might, however, be a useful place for the application of the ventouse.

It is sometimes possible to complete a delivery very rapidly with the ventouse, but when there is acute foetal distress a forceps delivery, which is usually quicker, is the treatment we have generally employed, as advocated by deWatteville (1958) and Muller (1959). Where foetal distress is less urgent we have had satisfactory results with the ventouse, and, indeed, Malmström (1957b) claims that weak foetal heart sounds may be favourably influenced by the application of traction.

We have also felt it necessary to retain forceps delivery for the training of house-surgeons, since the ventouse is not yet, so far as we know, in use in this country in general practice. Two of our house-surgeons who have used the ventouse have, however, expressed their intention of employing the instrument in general practice, and we feel that, subject to such limitations as are recognized for the use of forceps in domiciliary obstetrics, there may well be a place for the ventouse in the patient's home.

One of the greatest recommendations for the use of the ventouse for assisted deliveries is its simplicity. However, despite the simplicity of the method it is of primary importance, as in all obstetric operations, that a careful assessment of the case, including an exact vaginal examination, should precede any operative intervention. In particular, the position of the head in the pelvis should be accurately determined, especially so that the optimal point of application of the ventouse may be selected.

Conclusions

Our experience with this new method has confirmed Snoeck's view that it is a valuable addition to the obstetricians' armamentarium. It can replace the use of forceps in a wide range of conditions. It has the advantage over forceps that it can be used to deal with the problem of delay in the first stage of labour. In some instances, however, the time required for delivery with the ventouse is a disadvantage, and for this reason we regard it as unsuitable in acute foetal distress. In premature labour, in our experience so far, the instrument has probably been as safe as forceps, though deWatteville (1958) suggests that it should not be used with premature babies.

Finally, though we are not prepared to follow the example of Pigeaud (1957) in using the instrument routinely in all normal deliveries, we agree with Rosa (1955), Sohie (1957), and others that the ease and safety of application are strong recommendations for using it freely.

Summary

The use of the vacuum extractor (ventouse) in obstetrics is described and the literature surveyed.

Our experience of 100 cases delivered by means of the Malmström instrument is recorded.

It is considered that the instrument is safe for mother and child and can effectively replace the obstetric forceps in most instances except where there is acute foetal distress or a material degree of cephalopelvic disproportion.

In addition, it can be used during the first stage of labour to augment pains and promote dilatation of the cervix so that early delivery becomes possible.

Rotation of the occipito-posterior or transversely arrested head can in most instances be more easily and more physiologically effected with the ventouse than either manually or with forceps.

We are indebted to our colleague Mr. A. T. Marshall for help and criticism of this paper and for permitting us to quote results in several of his cases in the above series. We are grateful to Mrs. Joan Knowles for Fig. 2.

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PERSISTENCE OF ANTIBODY IN ADOLESCENTS AND ADULTS AFTER A THIRD, BOOSTER, DOSE OF POLIOMYELITIS VACCINE

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In previous reports (Reports, 1958, 1959) results were given of the neutralizing antibody responses obtained in a group of public-school boys and medical personnel after immunization with inactivated poliomyelitis vaccine. The subjects, none of whom had detectable antibodies to any of the three types of poliovirus before immunization, were given two injections of vaccine four weeks apart and a third, booster, injection 6 to 12 months later; serum samples were taken two weeks after the third dose. Further tests have now been made with the same group to determine the persistence of antibody after periods of up to two years.

Methods

Samples of serum were obtained from 46 of the schoolboys and from eight of the medical personnel at 18, 21, or 24 months after the third dose. They were titrated for neutralizing antibody in parallel with the serum samples taken two weeks after the third dose, all sera being tested against each virus type at one time. The galactose colour test was employed (Perkins and Evans, 1959), using fourfold serum dilutions in 0.25-ml. amounts, mixed with 100 $TCID_{50}$ of virus in 0.25 ml. All dilutions were made in Hanks solution and two cell-culture tubes were used for each serum dilution. Titres are expressed as the reciprocal of the initial dilution of serum protecting 50% of the tubes from virus action.

A fourth dose of 2 ml. of vaccine was given to those subjects whose antibody to type 1 had fallen to an undetectable level. The antibody responses to this dose were determined two weeks later.

At the time of taking the serum samples, saliva was obtained from some of the boys. After incubation at 56° C. for 30 minutes, 0.25 ml. of the twofold and eightfold dilutions were mixed with 10–30 $TCID_{50}$ of virus and, after 3½ hours' incubation at 37° C., added to prepared monkey-kidney-cell cultures, two tubes being used for each salivary dilution. Microscopical readings were taken after four days' incubation, as by this time the tubes had become acid.

Results

Figs. 1, 2, and 3 show the decline in serum antibody to each of the three types after the third dose of vaccine. After 18 to 24 months all 54 subjects had detectable

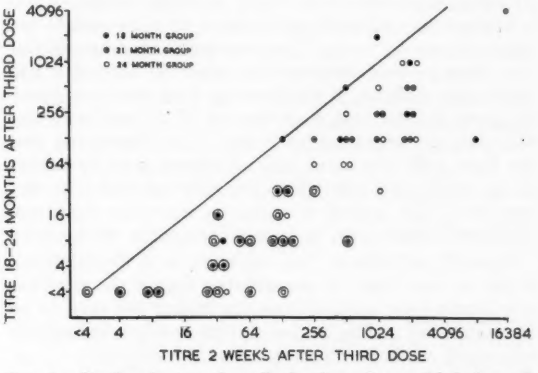

FIG. 1.—Decline in type 1 antibody titre after a third dose of poliomyelitis vaccine.

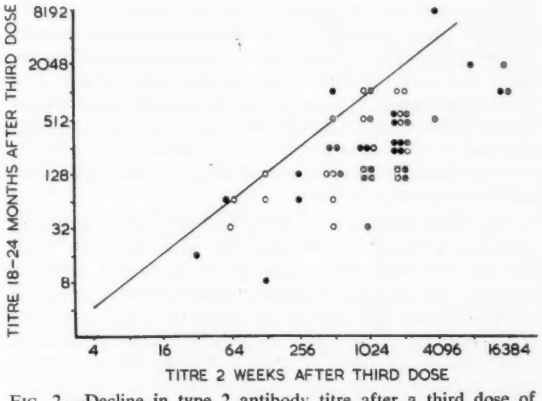

FIG. 2.—Decline in type 2 antibody titre after a third dose of poliomyelitis vaccine.

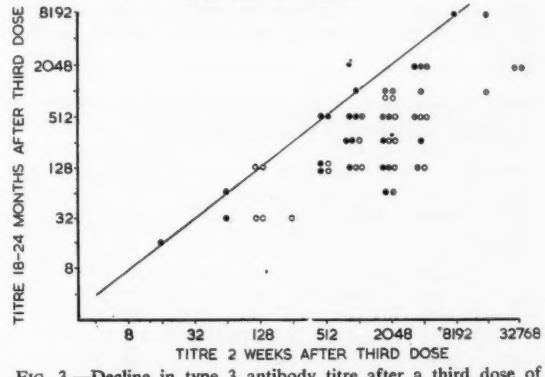

FIG. 3.—Decline in type 3 antibody titre after a third dose of poliomyelitis vaccine.

antibody to types 2 and 3 poliovirus, 44 showing titres of 128 or more to type 2, and 46 to type 3. However, 29 had type 1 antibody titres of 65 or less, and in nine of these antibody was undetectable at a titre of 4 and, on retitration, at a titre of 2.

These results can be related to the responses to the two primary cases and to the third dose of vaccine. Almost all 54 subjects had, at the time the third dose was given, measurable antibody to types 2 and 3 induced by the primary course and had responded well to the third dose. With type 1, however, 22 subjects had lost their antibody by the time the third dose was given and, compared with those who still had antibody, had tended to respond poorly to the third dose. The titres of those 22 subjects are shown in Fig. 1 by large circles, and it is evident that the antibody levels at 18 to 24 months are much lower—all being 32 or less and including eight of less than 2—than those of the other 32 who had had detectable antibody at the time the third dose was given. Of these 32 only four had titres of 32 or less, including one with no detectable antibody. It is interesting that the four with low titres had all shown poor responses to the third dose and before this injection had had very low titres (2), which may have been due to serum inhibitors rather than to true poliomyelitis antibodies.

Though individuals lost antibody at different rates, it can be seen that, in general, the higher the response two weeks after a third dose the higher the titre 18 to 24 months later. The decline of titre in a few individuals was small, while with others it was considerable.

Table I gives the geometric mean titres two weeks and 18 to 24 months after the third dose and the differences between the two. In general, the drop after 18 months was less than after 21 to 24 months. It was greatest in the 21-months group, whose mean response to the third dose was higher than that of the other groups. The average decreases in titre for all the subjects were similar for the three types, ranging from 76% for type 2 to 81% for type 1. Those subjects without detectable antibody were excluded from this calculation as their fall could not be determined.

The eight subjects who had lost their type 1 antibody after the primary course and also after the third dose did not respond well when given a fourth dose of vaccine. In six, the responses were definitely poor, all being less than 128, and in the other two only moderate —128 and 512. All eight subjects, however, responded satisfactorily to types 2 and 3, having titres ranging from 512 to 8,192.

There was no evidence, from the antibody levels obtained, that any of the subjects were naturally infected by any of the poliovirus during the period of this study.

TABLE I.—*Geometric Mean Antibody Titres of Groups of Schoolboys and Adults Two Weeks and 18 to 24 Months After a Third Dose of Poliomyelitis Vaccine*

Type	Titres at:				% Decrease in Titre	
	2 Weeks	18 Months	21 Months	24 Months	By Groups	For all Subjects
1	224	61	108	74	73	81
	812				87	
	425				83	
2	944	257	287	186	73	76
	1,560				82	
	676				73	
3	720	257	644	178	64	77
	3,780				83	
	870				80	

Of the samples of saliva tested for antibody to poliomyelitis virus, only 1 out of 21 inhibited type 1 virus, 4 out of 31 inhibited type 3, and none out of 25 inhibited type 2. None of the positive samples neutralized virus at a dilution of more than 4 and were from subjects with homotypic serum antibody titres of at least 2,048.

Discussion

It is evident from these results that the persistence of antibody and the level maintained after a third dose of poliomyelitis vaccine were dependent on whether detectable antibody was present at the time of the third dose, and this in turn depended on the potency of the vaccine used for the initial two doses (Salk, 1958; Kendall *et al.*, to be published). The vaccines used throughout these studies (Reports, 1958, 1959) were the best available to us, but in spite of this a proportion of subjects maintained detectable type 1 antibody levels for only short periods after the third dose, and even when given a fourth dose produced antibody responses which were similar to those which had been shown not to persist after the third dose.

The average fall in titre for all types after the third dose was from 76 to 81% in 18 to 24 months, and very similar to that found after natural infection by Lennette and Schmidt (1937). Their results indicated that, after type 1 infection, homotypic neutralizing antibody fell on the average to 25% of its peak value after a year, to 21.5% after 18 months, and to 18% after two years. The degree of fall during two years was negligible in some subjects, in others it was over tenfold. From our studies, as the number of subjects in each of the three groups are small, it was not possible to be certain if antibody declined after a booster dose at a constant date or decreased more slowly after an initial quicker fall. But mean titres at the three times of bleeding did seem to show that the average rate of antibody decline was not decreasing appreciably (Table I). The titres of some of the subjects had dropped very little over the study period and were similar to the examples given by Salk (1958), while a few had declined by as much as 12-fold. In the three groups of children studied by Salk, and who received vaccines of different potency, the average decline of antibody of each group during the year after a booster dose varied from a little over twofold to more than eightfold, and in those receiving poor vaccine a fifth had lost the type 1 antibody induced by the booster dose. All these findings indicate that antibody decline varies considerably from one individual to another.

Even if the subsequent average decline in antibody is somewhat slower than that occurring initially after infection or vaccination, it must be stressed that many subjects lose antibody very much faster than the mean. In determining vaccine schedules for the future these latter subjects are of most importance, as the intervals at which people should be given booster doses depend on how long they can maintain antibody in their circulations. Thus, if we presume that the average antibody fall found by us is continued, titres would reach, after an interval of about five years, a level of 1% of the post-third-dose titres (Fig. 4). In order to maintain detectable antibody and thus ensure that a fourth dose of poliomyelitis vaccine is effective when given after this interval—which is the interval adopted with other prophylactics (Wellcome Foundation, 1960)—titres of more than 100 for all three types should be attained after the third dose. At the present time, however, three doses of the better commercial vaccines are producing

in triple-negative subjects such titres to type 1 in only 70–75%, but to types 2 and 3 in almost 100%. This group of subjects accounts for at least half of all those paralysed and is the most difficult to immunize with inactivated vaccine.

The lowest titre found by us to be produced by natural poliomyelitis infection was 100; it was also the lowest titre after the third dose in the subjects studied here which ensured detectable antibody two years later or a good antibody response to the fourth dose, and the

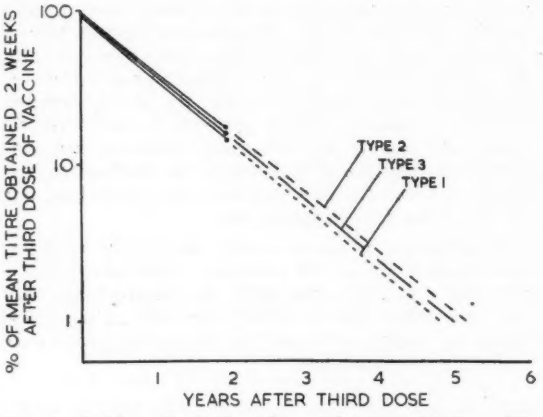

FIG. 4.—Fall in antibody titre after a third dose of poliomyelitis vaccine.

lowest titre obtained from a third dose after the use for the initial injections of a vaccine of sufficient potency to give detectable antibody to all types in 95% of subjects at the time of the booster dose.

Until evidence is produced to the contrary, it must be assumed that killed poliomyelitis vaccine protects only as long as antibody remains in the circulation, and it is generally agreed that this is the object of vaccination (Wellcome Foundation, 1960). Thus, from the antibody results reported here, the protection afforded by the best commercial vaccines for a five-year period can be estimated after three doses and after a fourth given within two years of the third. These estimated values, which are consistent with the 90% protection being found in the field after three or more doses over a shorter period (Poliomyelitis Surveillance Report, 1959), are given in Table II and indicate that protection would probably be increased from 84 to 95% if four instead of three doses were given.

TABLE II.—*Predicted Maximum Five-year "Protection" After Three and Four Doses of Inactivated Poliomyelitis Vaccine*

	Type 1*		Type 2	Type 3	Predicted Five-year Protection as Judged by a Titre of > 100 to All Types
	A	B			
Distribution of paralytic cases by virus type in unvaccinated subjects	50	30	5	15	
Percentage of vaccinees with a titre of > 100 after 3 doses	72	97	100	94	84%
No. of paralytic cases prevented after 3 doses	36	29	5	14	
Percentage of vaccinees with a titre of > 100 after 4 doses	90	100	100	100	95%
No. of paralytic cases prevented after 4 doses	45	30	5	15	

* Subjects without (A) and with (B) type 2 antibody before infection or vaccination.

It is questionable whether the effort required to give a fourth dose, within a year or two of the third, to the community at large is justified by this increase in protection, especially in those who are regularly vaccinated with other prophylactics and who will be receiving poliomyelitis vaccine at the same time. It would probably be of more general value first to encourage those subjects who have had only one or two doses of vaccine to complete the full schedule of three doses. If, however, vaccine with more potent type 1 component can be made, consideration of a fourth dose shortly after the third would be unnecessary. With present vaccines, a fourth dose should be given to those at special risk or when increased protection is particularly desirable. In such cases the optimum vaccination schedule is two doses four to six weeks apart, a third six to nine months later, and a fourth six to nine months after the third.

The results given here were obtained in adolescents and in adults, in whom the primary vaccination course may be somewhat less effective than in children (Report, 1958). The conclusions drawn are perhaps on the cautious side for this age-group, but are applicable to the other age-groups who are now being offered vaccination against poliomyelitis.

Summary

A study in 54 adolescent and adult subjects showed that neutralizing antibodies to types 2 and 3 persisted at a much higher level than antibody to type 1 when tests were made 18 to 24 months after a third dose of poliomyelitis vaccine.

The persistence of antibody after the third dose was shown to be dependent on whether antibody induced by the two primary doses of vaccine was present at the time the third dose was given.

The relation of these findings to the efficacy of vaccination is discussed.

Thanks are due to the Headmaster of Epsom College and to the boys who participated in this study; to Miss O. Stanbridge for technical assistance; and to the Ministry of Health for the vaccine used.

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"The fact is that the study of the causes and prevention of crime is in its infancy. We must learn as we go along. We are concerned not only with personal characteristics that make some people more prone than others to become delinquent. Our study must embrace also those elements of our society, products of our history, traditions, and outlook, which provide the incentive to crime. As a preliminary step I recently invited to a conference a number of academic authorities from several universities, in the various sciences touching on delinquency. As a result of their valuable help I am hopeful that new research projects may be started and that we may at last begin to tackle these most fundamental of all our problems." (*Penal Reform and Research*: Eleanor Rathbone Memorial Lecture by Mr. R. A. Butler, Liverpool University Press, 1960.)

PERSISTENCE OF ANTIBODY IN CHILDREN AFTER A THIRD DOSE OF POLIOMYELITIS VACCINE AND THEIR RESPONSE TO A FOURTH

BY

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During the 1956 field trial of inactivated poliomyelitis vaccine in the United Kingdom, 196 children between 1 and 10 years of age who had no antibody to any of the three types of poliovirus were tested for their response to vaccination by titrating the neutralizing serum antibodies induced by two doses of vaccine. A year later 107 of these children were given a third dose, and the antibody response was again determined (Medical Research Council, 1957a, and 1957b).

Further tests have now been made on 27 of these children to find out whether they still had antibody two years after the third dose. They were all given a fourth dose of vaccine and the antibody response of 25 of them was tested. Tests were also made to detect the presence of inhibitors to poliovirus in the faeces of these children.

Methods

Serum samples were taken at the same time as the children received the fourth dose of 1 ml. of poliomyelitis vaccine (Burroughs Wellcome Batch 17) intramuscularly into the upper arm. A second serum sample was taken 14 days later.

Most sera were titrated both by the cytopathic tests used routinely in the Virus Reference Laboratory, Colindale, and by the galactose colour test used in the Biological Standards Control Laboratory, Hampstead, in order to compare the titres obtained by each method.

In both methods, each serum was titrated, using two culture tubes for each dilution, except those from eight subjects whose sample of the post-third dose serum was still available. These sera were tested by the colour test together with the previous samples, using four tubes at each fourfold serum dilution. This was done in order to obtain a more accurate result of the antibody decline between the third and fourth doses from the few pairs of sera available. Titres are expressed as the reciprocal of the initial dilution of serum protecting 50% of tubes from virus action.

Colindale Cytopathic Test.—0.1 ml. of each fourfold serum dilution was mixed with 0.1 ml. of virus solution containing 200 $TCID_{50}$ of poliovirus of the type being used in the test. After three hours' incubation in a 37° C water-bath, the serum–virus mixtures were inoculated in 0.1-ml. amounts into monkey-kidney-cell roller cultures containing 1 ml. of Parker 199, and incubated at 37° C. for six days. The end-points of neutralization of virus by the serum dilutions were determined microscopically.

Hampstead Galactose Colour Test.—0.25 ml. of each fourfold serum dilution was mixed with 0.25 ml. of virus suspension (100 $TCID_{50}$) and placed in a 37° C. air incubator for six hours and then held overnight at 4° C. 0.5 ml. of a suspension of secondary monkey-kidney cells in lactalbumin solution were then added to each tube and the cultures sealed with liquid paraffin and incubated at 37° C. As galactose replaces glucose in the technique no colour change occurs during incubation. After five days a glucose solution was added and end-points were determined by the colour change. Cultures containing enough antibody to neutralize the virus, and protect the cell sheet, produced acid and turned the phenol-red included in the medium yellow. Those in which the virus had not been neutralized and destroyed the cells remained red.

Examination of Faeces.—10% suspensions of faeces were made in Parker 199 solution. After centrifugation at 5,000 r.p.m. for one hour the supernatants were removed, inactivated at 56° C. for half an hour, and tested for inhibitors to each of the polioviruses by the Colindale cytopathic test.

Results and Conclusions

The figures of the serum titrations by both methods are given in Table I. The results were parallel within the limits of the experimental error of each test. The actual titres were usually higher by the colour test, owing to the larger amounts of serum used at each dilution to neutralize the same amount of poliomyelitis virus and the longer time of neutralization before adding cells. Thus the sera found negative by the Colindale cytopathic test had low antibody levels by the Hampstead colour test. There was no evidence to suggest that the colour test was detecting low-avidity antibody and the cytopathic test high-avidity antibody (Sabin, 1958). If there are two such antibodies, either test can be adjusted to measure them by varying the temperature and length of incubation of the virus–serum mixtures before they are brought into contact with the monkey-kidney cells. Higher titres of poliomyelitis antibody can more easily be obtained with all sera containing them if neutralization is allowed to run at 37° C. for a few hours than if only one hour at room temperature is selected (Perkins *et al.*, 1958).

From Table I it can be seen that two years after a third, booster, dose of poliomyelitis vaccine all except perhaps one (V.C.) out of 27 children still had detectable serum antibody to all three types, as determined by the colour test. With type 1 the levels ranged from 4 to 1,024, with type 2 from 64 to 1,024, and with type 3 from 8 to 4,096. In the one exception, the amount of serum available was so small that a full type 1 titration could not be done; however, type 1 antibody was not detectable at a dilution of 1/16 and in all probability was entirely absent, since an indifferent response was obtained to the fourth dose in both tests. With exception of this subject, the response to all the components of the vaccine was good after the fourth dose and similar to that after the third (M.R.C., 1957b). Only one of the subjects had lost antibody before the third dose, and

TABLE I.—*Comparison of Antibody Titres Obtained by Two Methods of Titration Before and After a Fourth Dose of Poliomyelitis Vaccine*

Subject	Type 1				Type 2				Type 3			
	A1	B1	A2	B2	A1	B1	A2	B2	A1	B1	A2	B2
P.C.A. ..	64	16	128	256	128	64	512	512	128	64	128	256
M.A.A. ..	32	32	512	2,048	128	256	256	4,096	32	64	512	1,024
A.J.A. ..	<4	4	64	1,024	64	64	1,024	4,096	32	64	512	1,024
A.C.B. ..	128	256	1,024	4,096	512	512	1,024	1,024	64	512	512	2,048
B.K.B. ..	32	256	128	256	128	256	256	1,024	32	64	128	1,024
G.R.B. ..	16	32	128	256	32	64	256	1,024	<4	64	64	512
B.A.B. ..	32	256	512	—	256	1,024	1,024	—	128	128	512	—
A.E.B. ..	128	512	512	4,096	128	256	512	4,096	32	16	512	2,048
B.F.B. ..	32	512	128	4,096	512	256	4,096	4,096	1,024	4,096	8,192	8,192
J.P.B. ..	<4	16	128	4,096	128	256	512	2,048	64	256	1,024	4,096
M.J.B. ..	<4	8	16	256	32	64	2,048	1,024	128	256	128	128
C.J.B. ..	64	64	512	4,096	32	64	2,048	4,096	32	16	256	512
P.S.B. ..	128	256	128	1,024	128	256	256	2,048	4	8	128	1,024
S.C. ..	<4	4	<4	256	512	256	512	1,024	128	64	128	128
V.C. ..	—	<16	32	128	—	128	64	1,024	—	16	128	1,024
D.A.D. ..	512	1,024	512	2,048	128	64	256	1,024	128	64	512	2,048
G.J.E. ..	<4	4	32	—	128	256	256	—	<4	16	256	—
S.N.G. ..	<4	16	128	1,024	64	128	512	2,048	4	16	128	1,024
A.B.H. ..	64	256	256	2,048	128	256	1,024	4,096	256	1,024	512	1,024
B.R.H. ..	8	64	128	2,048	128	512	256	1,024	128	64	256	1,024
H.N. ..	64	256	64	—	64	64	128	—		256		—
C.E.S. ..	8	32	512	1,024	8	64	1,024	4,096	256	32	256	2,048
D.S.S. ..	128	1,024	256	1,024	512	256	1,024	4,096	512	512	2,048	4,096
D.B.V. ..	16	128	128	1,024	256	256	256	1,024	64	256	128	1,024
F.A. ..	4	64	—	—	128	256	—	—	128	512	—	—
P.A. ..	<4	4	—	—	128	1,024	—	—	32	128	—	—
F.B. ..	128	1,024	256	—	128	512	1,024	—	128	256	256	—
Geometric mean titre*	16	69	137	1,060	112	195	535	1,860	53	103	309	1,060

* Only those sera titrated by both methods used for the mean titre calculation.
A1 and A2: Titres obtained before and after vaccine by Colindale cytopathic test. B1 and B2: Titres obtained before and after vaccine by Hampstead galactose colour test.

to type 1 only. It can therefore be concluded that the three vaccines used in the British field trial produced a good level of primary immunization and were as potent as any that have been used since in this country.

Table II shows the decline in the antibody titre of eight children during the two years between their third and fourth doses. The titres declined at different rates in different subjects, but the rate for all types was approximately similar in any individual. The average fall was 4.8-, 4.6-, and 4.7-fold for types 1, 2, and 3 antibody respectively, a result similar to that found in adolescents and adults by Kendall *et al.* (1960). Two of the children showed a rise in antibody to one type between the third and fourth doses, a rise which was greater than could be accounted for by the error of the colour test (Mussett and Tobin, to be published) and could have been due to natural infection; they were therefore excluded from the calculation of the mean titre.

The question of natural infection augmenting the response to vaccine must be considered when studying persistence of antibody after vaccination. Only when samples of serum taken at the beginning and end of the observation period are tested, and the subjects themselves belong to a community free from infection during the study period, can results be conclusive. These criteria have been realized in the studies conducted at public schools (Medical Research Council, 1959; Kendall *et al.*, 1960), but are difficult to obtain in those of the general public. However, the levels of titres recorded here before revaccination are such that they are unlikely to be due to natural infection but are rather what one would expect after the good response obtained to the third dose in this group of children (M.R.C., 1957b).

TABLE II.—*Decline in Poliomyelitis Antibody During a Two-year Period Between the Third and Fourth Doses of Vaccin.*

Subject	Type 1		Type 2		Type 3	
	Post 3rd Dose Titre	Pre 4th Dose Titre	Post 3rd Dose Titre	Pre 4th Dose Titre	Post 3rd Dose Titre	Pre 4th Dose Titre
P.C.A. ..	512	32	1,536	512	1,024	128
A.J.A. ..	256	8	1,024	64	512	64
A.C.B. ..	1,024	256	256*	768*	768	512
B.K.B. ..	48*	256*	512	256	512	96
G.R.B. ..	256	32	512	64	512	96
B.A.B. ..	512	256	2,048	512	512	128
B.F.B. ..	512	256	512	512	2,048	1,536
C.J.B. ..	256	32	1,024	64	1,024	64
Geometric mean titre	420	87	890	192	763	163
Ratio of means ..	4·8		4·6		4·7	

* Rise greater than could be accounted for by error in colour test. Excluded from calculation of mean titre.

No inhibitors to any of the poliovirus types were found in the faeces of any of these subjects, either before or after vaccination, in spite of the high antibody titres appearing in the blood of most subjects. Thus vaccination does not appear to produce the faecal inhibitors described by Steigman and Lipton (1959) after natural infection. Similar experiments made on the saliva of vaccinated schoolboys also gave negative results except in rare cases, when the serum antibody titre was exceptionally high (Kendall *et al.*, 1960). These findings support the conclusions of Gelfand *et al.* (1957) and of Davis *et al.* (1958), that vaccination with killed vaccine is unlikely to reduce the spread of the poliomyelitis virus in the community and that protection against paralysis must come directly from the adequate immunization of each individual.

Summary

The poliomyelitis antibody level in 27 children was measured two years after they had received a third dose of inactivated poliomyelitis vaccine. The children still had demonstrable antibody in their serum against the three polioviruses except for one who appeared to lack type 1 antibody. The antibody fall during the two years was estimated to be 78–79% for all three virus types.

A good response to a fourth dose of the inactivated vaccine was found in most of the children.

No poliovirus inhibitors could be found in the faeces of these children either before or after the fourth dose.

A comparison was made of two different methods of titrating poliomyelitis antibodies.

Our thanks are due to the children who participated in this investigation and to their parents for permission to take serum samples.

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NUCLEAR CHANGES IN SQUAMOUS CELLS FROM BUCCAL MUCOSA IN PERNICIOUS ANAEMIA

BY

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In a previous communication evidence was briefly presented which confirmed the existence of abnormally large nuclei in oral squamous mucosa in pernicious anaemia (Farrant, 1958a). The present paper gives the results obtained by examining a series of patients with pernicious anaemia before and after treatment. In addition, further comparison of patients with pernicious anaemia and normal subjects has disclosed differences in nuclear shape and in variability of size.

Materials and Methods

Films of oral mucosa were obtained by scraping the inside of the right cheek with an ordinary microscope slide. The resulting material was spread on to a further slide, dried in air, fixed, and then stained by a standard technique (May–Grünwald–Giemsa). An image of the buccal squamous cells and their nuclei was projected by means of a microscope and a powerful source of light on to a ground-glass screen arranged so as to give a magnification of 1,000. Measurements were made in the centre only of this optical system in order to minimize the effects of spherical aberration. It was found difficult to measure the size of the squamous cells themselves because of their irregular outline. The squamous-cell nuclei, on the other hand, have a relatively uniform oval shape, and accordingly 100 nuclei in each preparation were examined and measured. The measurements made were those of the long and short axes. For each axis the means of these 100 measurements were used for comparison. Though variation in mean nuclear size among normal controls is considerable, it was found that the mean nuclear measurements in different parts of the same slide, and different slides taken consecutively from the same person, varied by only a small amount.

Twenty-five patients with pernicious anaemia were examined both before and after treatment. Repeat films of oral mucosa were taken at intervals varying from 2 to 32 months after successful treatment. Criteria of diagnosis were the presence of a typical macrocytic blood film and of a megaloblastic marrow, the demonstration of a histamine-fast achlorhydria, and a satisfactory response to treatment with vitamin B_{12} or liver. In eight patients these diagnostic criteria were incompletely fulfilled. Four patients had no bone-marrow examinations made, one died as the result of a fractured femur before treatment of her anaemia became effective, while the rest had either no test meals or test meals which showed achlorhydria but without histamine stimulation. The haemoglobin concentrations in 24 patients after treatment varied from 12.5 to 17.2 g./100 ml., with a mean of 14.4 g. Blood films were either normal or showed minor degrees of anisocytosis. One further patient had a haemoglobin value of 11.5 g./100 ml., but developed some changes of iron deficiency in the blood film.

Results

The mean values of the nuclear measurements have been compared for each axis, both before and after treatment, and the differences calculated (see Table).

Effect of Treatment Upon Mean Nuclear Size

Case No.	Long Axis in Microns			Short Axis in Microns		
	Before Treatment	After Treatment	Difference	Before Treatment	After Treatment	Difference
1	11·93	12·34	+0·41	9·32	9·47	+0·15
2	13·15	12·48	0·67	10·50	9·01	1·49
3	12·88	11·57	1·31	10·30	8·78	1·52
4	9·74	10·92	+1·18	6·87	7·12	+0·25
5	11·53	11·71	+0·18	9·13	8·48	0·65
6	12·09	11·64	0·45	9·83	9·35	0·48
7	12·64	10·27	2·37	10·16	7·48	2·68
8	10·48	10·95	+0·47	7·95	7·98	+0·03
9	12·25	11·51	0·74	9·81	8·40	1·41
10	12·57	11·83	0·74	9·74	8·90	0·84
11	13·08	12·03	1·05	10·58	9·19	1·39
12	13·06	11·65	1·41	9·78	8·32	1·46
13	12·12	11·98	0·14	9·48	8·99	0·49
14	11·90	11·59	0·31	9·52	8·60	0·92
15	12·18	11·91	0·27	9·41	8·83	0·58
16	12·45	11·42	1·03	9·55	8·82	0·73
17	15·02	11·44	3·58	11·50	8·85	2·65
18	12·32	11·27	1·05	9·76	8·62	1·14
19	12·39	11·87	0·52	9·13	9·07	0·06
20	12·89	11·68	1·21	10·43	8·89	1·54
21	12·21	12·61	+0·40	9·73	9·61	0·12
22	12·26	11·49	0·77	9·64	8·50	1·14
23	14·04	12·05	1·99	11·52	9·19	2·33
24	11·99	10·30	1·69	9·60	7·72	1·88
25	11·15	11·55	+0·40	8·33	8·51	+0·18

In six patients the mean values in one or other axis are greater after treatment than before, but only in four of them is this effect shown in the measurements of both axes, the other two showing a diminution in size of the short axis. In three of the four cases (Nos. 4, 8, and 25) normal values were obtained for both axes before treatment and one would therefore hardly expect any diminution in nuclear size after treatment. The fourth case (No. 1) showed only a minor degree of anaemia (12.1 g./100 ml.), and has been treated and maintained on an oral preparation of vitamin B_{12}. In all these four patients the increase in nuclear size after treatment is comparatively small. The remaining 19 patients all show varying degrees of diminution in nuclear size in both axes.

The results from these 25 patients with pernicious anaemia have been expressed for each axis as a frequency distribution curve. These show (Figs. 1 and 2) a highly significant decrease in nuclear size after treatment, the decrease being greater in the short axis. A population of larger nuclei among the untreated patients is also disclosed. Not only do the nuclei become smaller and more uniform in shape when specific treatment is given to a patient with pernicious anaemia, but in many cases the nuclear chromatin becomes more pyknotic and dense (Figs. 3 and 4).

This difference in the appearance of the nuclear material is reminiscent of the changes seen in the red-cell precursors in pernicious anaemia before and after treatment. An experiment was therefore made to test the local effect of vitamin B_{12} on the squamous-cell nuclei in untreated pernicious anaemia. Horrigan, Jarrold, and Vilter (1951) have already demonstrated an effect of local vitamin B_{12} on the bone-marrow in pernicious anaemia. With suitable controls a very small dose of vitamin B_{12} was injected into the oral mucosa of a patient with untreated pernicious anaemia, but no conclusive reduction in nuclear size was shown.

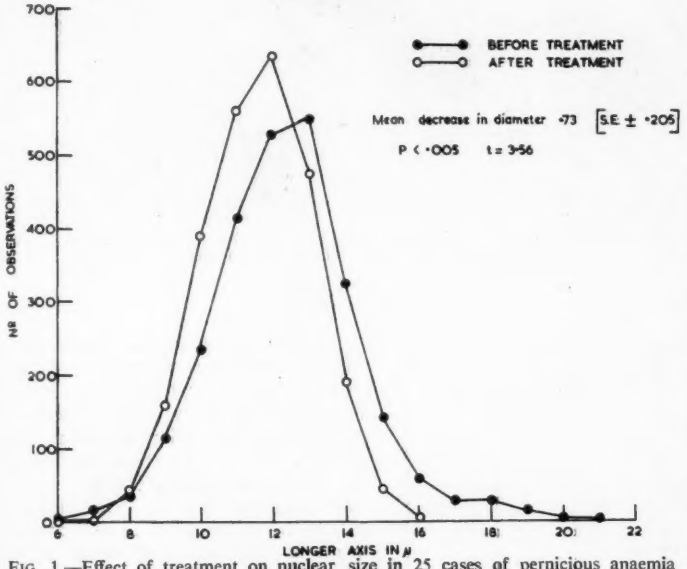

FIG. 1.—Effect of treatment on nuclear size in 25 cases of pernicious anaemia (long axis).

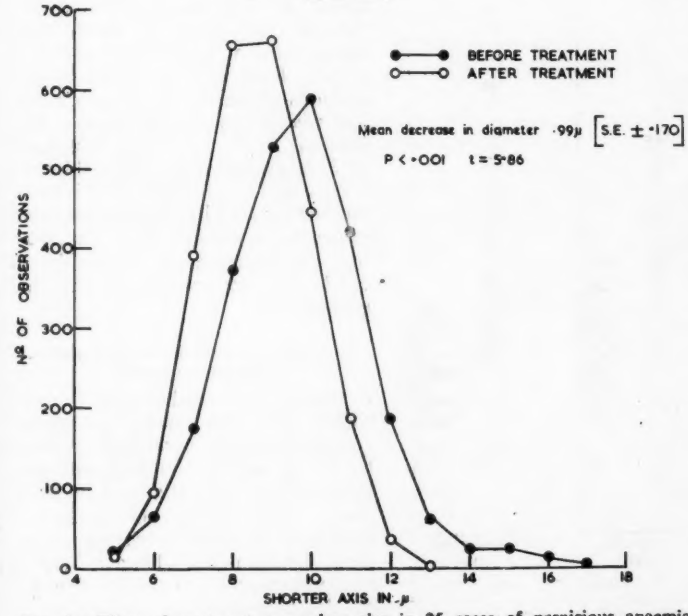

FIG. 2.—Effect of treatment on nuclear size in 25 cases of pernicious anaemia (short axis).

Nuclei of Abnormal Shape

In pernicious anaemia not only are the squamous-cell nuclei abnormally large but in addition they may have an irregular asymmetrical outline. In 28 out of 39 patients with pernicious anaemia previously examined abnormal nuclei were found, varying in incidence from 1 to 15 per 100 nuclei examined. The overall incidence in all patients was 3 per 100 nuclei. There was no correlation between mean nuclear size and the number of such abnormal nuclei observed. In contrast to these findings in untreated pernicious anaemia, 25 cases have been examined again after treatment, and among these, and among 62 normal subjects, only two abnormal nuclei were seen, one being found in each group.

Variability in Nuclear Size in Pernicious Anaemia and Normal Subjects

The values for the standard deviation in each set of 100 nuclear measurements have been calculated in 39 cases of pernicious anaemia, in 62 normal subjects, and in the 25 patients who have been studied both before and after treatment. The variability of nuclear size was significantly less among normal individuals and treated cases than among untreated cases of pernicious anaemia (Figs. 5 and 6). Thus not only are squamous-cell nuclei abnormally large in pernicious anaemia but their variation in size is greater than normal. Both values, those of mean and of standard deviation, revert towards normal with treatment.

Evidence has already been presented (Farrant, 1958b) that there is no effect of anaemia itself, of oral sepsis, or of achlorhydria in the absence of pernicious anaemia, on the size of squamous-cell nuclei from the mouth. Results among 95 normal subjects previously studied have been analysed according to the factors of sex, smoking, and, where relevant, position in the menstrual cycle. No association between any of these factors and squamous-cell nuclear size has been found.

Discussion

Relationship of Nuclear Changes to Disordered Metabolism in Pernicious Anaemia

It has been shown that nuclear abnormalities are found in oral epithelium in pernicious anaemia. The nature of these changes and their response to treatment

suggests a parallel with changes found in pernicious anaemia in the myeloid and erythroid tissues. There is much evidence for a disorder of nucleic-acid metabolism in this type of anaemia. Such a disorder may be responsible for changes in the red cells and white cells of bone-marrow and blood. Riddle (1929) has suggested that purine and pyrimidine metabolism is abnormal in pernicious anaemia, and James and Abbott (1952), during a study of urinary phosphorus excretion, concluded that the reappearance of normoblastic erythropoiesis was accompanied by the rapid formation of nucleotides.

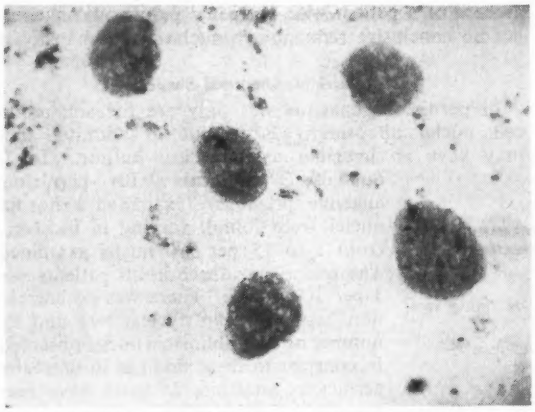

FIG. 3.—Pernicious anaemia (Case 17). Photomicrograph of oral mucosa before treatment. (×570.)

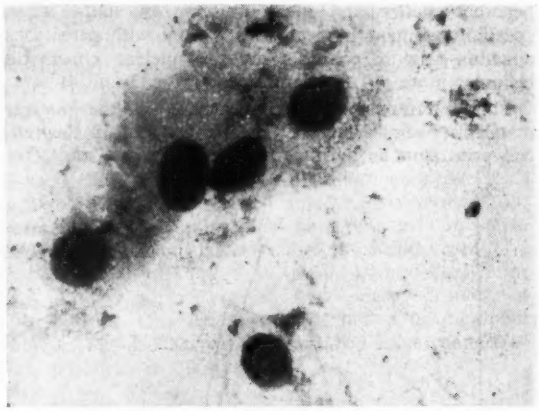

FIG. 4.—Pernicious anaemia (Case 17). Photomicrograph of oral mucosa four months after treatment. (×570.)

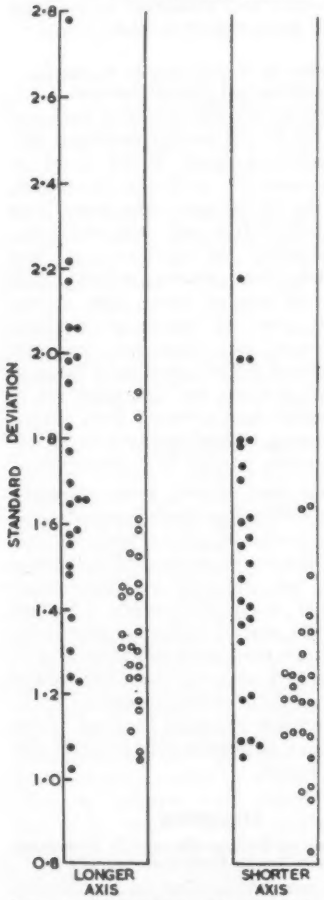

FIG. 5.—Comparison of standard deviation before (●) and after (○) treatment in 25 cases of pernicious anaemia.

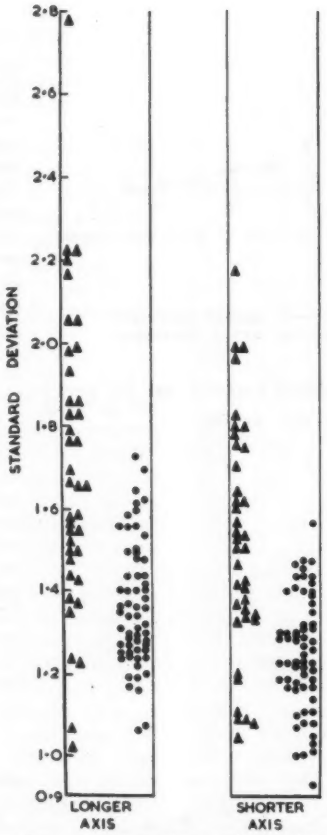

FIG. 6.—Comparison of standard deviations in untreated pernicious anaemia and in normal controls. ▲=P.A. ●=Controls.

Attempts to provide an explanation of the interaction of folic acid and vitamin B_{12} in nuclear metabolism have been made by Vilter, Horrigan, Mueller, Jarrold, Vilter, Hawkins, and Seaman (1950) and by Nieweg, Faber, de Vries, and Kroese (1954). It has been suggested (Smith, 1958) that the action of vitamin B_{12} on protein synthesis may occur by virtue of its effect on a number of enzyme reactions. It is not clear, however, why deficiency of vitamin B_{12} should cause enlargement of certain cells and their nuclei. From a study of the relative amounts of desoxyribose nucleic acid and ribonucleic acid in vitamin B_{12}-deficient livers, Rose and Schweigert (1952) suggested that a reduced rate of nucleic-acid synthesis in turn reduced the rate of cell division, thus corroborating the hypothesis of Castle (1953) that the consequence of inability to divide was enlargement of cell and nucleus.

Abnormal Epithelial Cells and Nuclei in Pernicious Anaemia

Massey and Rubin (1954) have shown that the nuclei of gastric columnar cells in pernicious anaemia tend to be abnormally large, and that these changes are not altered by treatment. When studying the cytology of specimens obtained by gastric aspiration, Graham and Rheault (1954) observed that the cytoplasmic diameter of desquamated squamous cells in pernicious anaemia became smaller

after specific treatment. Boen (1957) has studied similar changes in mouth washings from cases of pernicious anaemia. A small series of patients and normal controls was studied, and the mean long diameter of the squamous-cell nucleus in certain of his cases was found to be abnormally large. Boddington (1959) has confirmed that enlargement of the nuclei from desquamated oral epithelial cells occurs in megaloblastic anaemia. More particularly this enlargement is related to epithelial atrophy of the tongue. Such a relation was not noted in this work (Farrant, 1958b), but the recognition of minor degrees of atrophy is difficult. In addition the epithelia studied may not be comparable.

In the present study variability of nuclear size in buccal epithelium has been found to be increased, and this is at least as characteristic a change as that of greater mean size in pernicious anaemia. In his study of the diameter of red blood cells in pernicious anaemia, Price-Jones (1933) found a correlation between variability of red-cell size and the number of red cells, and a less strict correlation between variability of size and haemoglobin level. He also noted that the mean size of the red cells, as opposed to their variability, bore no relation to the degree of anaemia. The present work has shown that the size of squamous-cell nuclei, too, is independent of the degree of anaemia.

The change to normal size and shape of the nuclei was observed to occupy only a few days once treatment in pernicious anaemia was started. Not infrequently a longer time may be needed for a smooth tongue to become normal. If enlargement of squamous-cell nuclei is a consequence of failure of normal nuclear division, and if changes in the basal layer of the tongue are similar in nature to those found in buccal epithelium, then impairment of growth of cells at the base of the filiform papillae might occur. This would allow desquamation of cornified cells from the tip of the papilla to exceed regeneration from below, and papillary atrophy would result. Conversely, when treatment began and normal cell divisions started, the need for increased regeneration to exceed continuing desquamation might account for the delay in the return to normal of the lingual epithelium, as compared with the changes caused by treatment which have been demonstrated in this study. Impaired activity of the basal cell layer of the tongue has been demonstrated in the glossitis of pernicious anaemia by Taft, Hughes, and Wood (1958).

In a few patients with untreated pernicious anaemia the squamous-cell nuclei have been found to be of normal size. Vitamin-B_{12} deficiency may not always present in the same clinical form, and very low levels of serum vitamin B_{12} have been reported (Mollin and Ross, 1954) in a small group of patients with subacute combined degeneration of the cord in the absence of significant anaemia. Sanford (1935), Brown (1946), and Bastrup-Madsen (1954) have all described the simultaneous occurrence of oral and neurological manifestations with little or no anaemia. The patients with squamous-cell nuclei of normal size did not, however, differ from the others with regard to the incidence of glossitis or subacute combined degeneration of the cord, and a cause for the presence in them of nuclei of normal size was not discovered.

Summary

By measuring squamous-cell nuclei from the mouth, abnormalities of nuclear size, shape, and variability of size have been demonstrated in pernicious anaemia. Treatment causes these abnormalities to regress. The possible significance of these findings is discussed.

I am grateful to Professor C. Bruce Perry for advice and encouragement, to Dr. F. G. Bolton for continuing assistance and helpful criticism, and to Miss E. H. L. Duncan for invaluable statistical aid. The physicians and surgeons of the United Bristol Hospitals kindly allowed me to study their patients. Part of the work was carried out with the aid of a grant from the Board of Governors of the United Bristol Hospitals, which I most gratefully acknowledge.

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THE E.S.R. IN A NEW DRESS

BY

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The E.S.R. is one of the oldest investigations in clinical medicine, and appears to have developed in a crude form from observations on the blood in relation to "blood-letting." The first modern investigation of the diagnostic possibilities of the test was made by the Swedish physician Fåhraeus (1921, 1929), who attempted to make use of a raised E.S.R. as a diagnostic test for pregnancy. He failed in his thesis, but developed a method of E.S.R. estimation that his pupil Westergren, working with male tuberculosis cases in Stockholm, was later to improve upon and publish in his classical paper in 1921.

Other methods have since been tried, notably that of Wintrobe (1933), but for various reasons, not discussed here, they have fallen from favour, and the Westergren method and its values still form the foundations for present-day clinical thinking.

The substance of this paper arose from the gradual evolution of hybrid methods for estimating the E.S.R. (or, more exactly, the erythrocyte aggregation sedimentation rate) as a result of laboratory modifications of the classical Westergren method without any

apparent evaluation of their relative accuracy or revision of the standards used. The methods that had developed in Edinburgh were suspected of serious anomalies, and this communication represents an attempt to clarify the situation.

Practical and Theoretical Considerations

The numerical value of the E.S.R. is largely dependent on those factors which affect the red-cell surface and on the concentration and molecular shape of the associated serum proteins; hence, for example, the needle-like fibrinogen molecule will produce a higher E.S.R., weight for weight, than will the rounded molecule of albumin.

It is now generally believed that an accurate and reproducible E.S.R. based on known normal standards does, if elevated, indicate a non-specific somatic reaction to disease.

A comprehensive study of the multitude of factors that can affect the E.S.R. has been made by Nichols (1942), working with horses' blood; but for clinical purposes the main physico-chemical and other factors affecting the E.S.R. are more limited and include:

Major Factors.—(1) The dimensions of the tube used in the estimation itself. (2) The verticality of this tube. (3) The use with the blood sample of a liquid or a solid as an anticoagulant—for example, solid "sequestrene" (ethylenediaminetetra-acetic acid; E.D.T.A.), liquid citrate. (4) The technique associated with venepuncture, including trauma, contamination, and cleanliness of apparatus. (5) The total time over which the estimation is made.

Minor Factors.—(1) The time elapsing between withdrawing blood from the patient and testing it. (2) The anticoagulant chosen and the care taken in mixing in different cases. (3) The surrounding temperature *in moderate climates.* (4) The "reflux factor" of Alexander (1953). (5) The choice between arterial and venous blood samples and their gas content. (6) Personal factors—frustration, clumsiness, and fatigue.

It has been shown from past studies on the E.S.R. that when anticoagulated venous blood is subjected to all the above physico-chemical variants in a suitable tube it undergoes three major phases—aggregation, fall, and pile-up (Fig. 1).

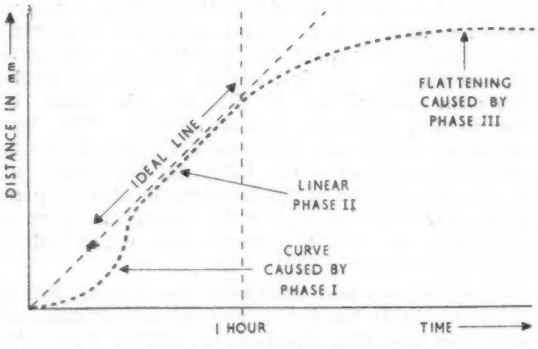

FIG. 1.—Showing curve during the three phases.

The first phase, that of red-cell aggregation, should be as short as possible. The reason for this is that measurement of the E.S.R. is, for sake of convenience, taken from the setting up of the tube, and not, as strictly speaking it should be, from the time when aggregation is complete and fall begins; and therefore phase 1, the formation of the aggregation, is included in the final result.

However, it is in the second phase that the chief interest lies, for this represents the falling of the red-cell aggregates under a steady gravitational influence which, ideally, is graphically linear. When this is so, it can reasonably be assumed that the forces involved are acting on a complete and stable state of aggregation, and the drop can then be read in one of two ways: either as time in minutes per millimetre unit of fall, or as fall in millimetres per unit time (one hour).

The third phase results from the effect on the falling red-cell column of its leading members piling up at the bottom of the tube, and this is a very real factor in rapid E.S.R.s. If, however, the tube is of reasonable length, then it is found that this phase does not affect the result over a one-hour period unless the aggregated fall is over some 30% of the tube length. This means that with a tube of 200 mm. a result of up to 70 mm. in one hour would be unaffected.

Against this background it became necessary to establish which was the most convenient method of determining the E.S.R. in a routine comprehensive haematological service.

Aims

1. To develop a method which would use sequestrene as an anticoagulant and to calibrate it against the standards of present accepted methods, and which would, in addition, conform with the following requirements: (*a*) It could be adapted from apparatus already in general use and ideally would employ present accepted normal standards. (*b*) It would be standardized on anticoagulated samples of venepuncture blood, both in technique and in equipment, and should be reproducible in any laboratory.

2. (*a*) To find a method of suspending a pipette so as to increase the accuracy of the E.S.R. estimation; this was essential owing to the very considerable effect any deviation from the vertical had on the reading obtained. (*b*) To develop a tube that would be cheaper, simpler, and less frustrating than the type in present use.

3. To compare the various methods involved in E.S.R. estimation: (*a*) "classical" and "modified classical Westergren"; (*b*) using undiluted blood with Heller's ammonium potassium (NH_4/K) oxalate as anticoagulant; (*c*) using undiluted blood with sequestrene as anticoagulant; (*d*), (*b*) and (*c*) repeated, but with an additional dilution with a 1 in 4 ratio of isotonic citrate/blood.

4. To investigate the effect on the result of delay between obtaining the blood sample and the carrying out of the E.S.R. estimation which is pertinent in a general practitioners' service where such a delay may amount to some seven to eight hours (9 a.m. to 4 p.m.).

5. To investigate less fully, and as a check on the excellent literature available, subjects such as: (*a*) the effect of contamination with spirit; (*b*) the preparation and concentration of the anticoagulant; (*c*) the cleanliness of the apparatus; (*d*) the relative accuracy of the apparatus used.

Materials and Method

The blood samples were obtained from male and female patients in two general medical wards of the Royal Infirmary, Edinburgh, and from a small number of patients attending the radiotherapy follow-up clinic

and the antenatal clinic in the Simpson Memorial Maternity Pavilion. The patients were selected for study because of the suspected abnormal level of their E.S.R. rather than for the nature of their illness, and the group was constituted as follows:

Age	Female (67 patients)	Male (68 patients)
10–19	3	6
20–29	1	7
30–39	9	4
40–49	15	5
50–59	14	12
60–69	13	12
70–79	11	11
80–89	1	0

Blood samples were obtained with minimal stasis and trauma from the antecubital vein, after cleansing of the skin with a small amount of methylated ether and allowing to dry. Dry sterilized siliconed 5-ml. and 20-ml. all-glass syringes fitted with syringe service 1½ in. (3.8 cm.) 20-gauge hypodermic Luer needles were used throughout.

After removal of the needle from the 20-ml. taking syringe, the blood was gently added to a glass "Wintrobe" tube, previously cleaned with detergent and chromic acid and then rinsed clean and oven-dried. The tube, containing either sufficient solid sequestrene or NH_4/K oxalate to prevent 3 ml. of blood from clotting, was then stoppered with either a "supa-seal" cap or a red rubber bung. A further 3-ml. sample was also added to a tube without anticoagulant, and 2 ml. of this blood was then immediately withdrawn from it into a 5-ml. syringe and added to 0.5 ml. of isotonic 3.8% citrate solution in a further tube, thus constituting an approximation to the classical Westergren method. Immediately after filling, all the tubes were slowly inverted five times to ensure efficient mixing of the contents.

The blood samples were then examined at the laboratory within the next one to two hours, except when separate samples were set aside for various fixed times before examination, in order to determine the effect of storage deterioration on the E.S.R.

In the laboratory the samples underwent further mixing by inversion some 15 to 20 times, and portions were then taken from these tubes in one of three different ways:

1. Sufficient was sucked directly and undiluted into a Westergren pipette.

2a. 2 ml. was sucked into a 2-ml. bulb pipette and subsequently expelled into a second tube containing 0.5 ml. of isotonic citrate which had previously been accurately added from a microburette, the resulting 1 in 4 dilution being finally mixed by expelling from and sucking into the pipette at least twice.

2b. 2 ml. was sucked into a 2-ml. graduated pipette which had previously been used to introduce 0.5 ml. of isotonic citrate solution into an empty tube, and this blood was added to the citrate solution, mixing once more being achieved by sucking up and down as before, again producing a 1 in 4 dilution.

Once these diluted samples 2a and 2b had been prepared, Westergren pipettes were filled, each pipette requiring about 1 ml. of blood. One set of pipettes was filled in the standard manner and set up in the normal stand, using rubber cushions and spring-clips, while a second set of pipettes was suspended from hooks, using a very simple gimbal suspension (Fig. 2) designed by Dr. Duxbury, of Chase Farm Hospital, the distal ends of the tubes being blocked by cystoscope caps of soft red rubber.* Fig. 3 shows the Weyroc board for suspending the pipettes.

The blood was sucked into the pipette to above the zero mark and allowed to fall back in the usual way, thus satisfying any reflux effects, and, with the tube then held almost horizontally in the master-hand with the

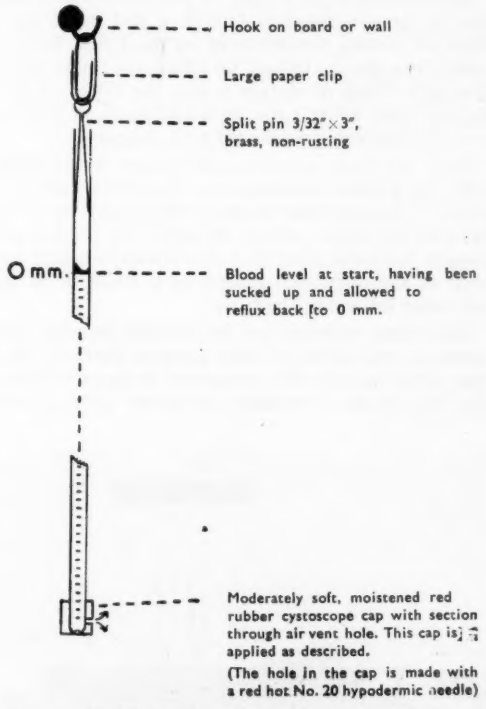
Hook on board or wall
Large paper clip
Split pin 3/32"×3", brass, non-rusting
O mm.
Blood level at start, having been sucked up and allowed to reflux back to 0 mm.
Moderately soft, moistened red rubber cystoscope cap with section through air vent hole. This cap is applied as described.
(The hole in the cap is made with a red hot No. 20 hypodermic needle)

FIG. 2.—Modified tube with simple gimbal mounting.

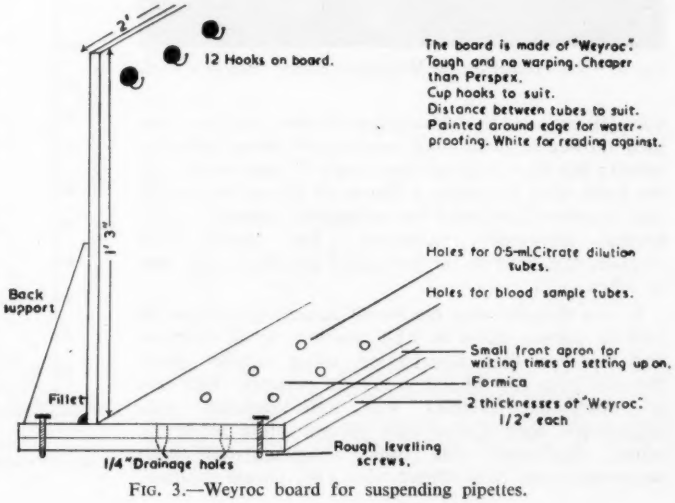
2'
12 Hooks on board.
The board is made of "Weyroc". Tough and no warping. Cheaper than Perspex.
Cup hooks to suit.
Distance between tubes to suit.
Painted around edge for water-proofing. White for reading against.
1' 3"
Back support
Holes for 0·5-ml. Citrate dilution tubes.
Holes for blood sample tubes.
Small front apron for writing times of setting up on.
Formica
2 thicknesses of "Weyroc" 1/2" each
Fillet
1/4" Drainage holes
Rough levelling screws.

FIG. 3.—Weyroc board for suspending pipettes.

*These non-perforated caps were obtained from the Genito-Urinary Mfg. Co. Ltd., 33–34, Devonshire Street, London, W.1.

forefinger over the upper end, a red rubber cystoscope cap, previously moistened with water, was slipped over the lower end of the pipette until the lower end impacted on the cap with the air-escape hole uppermost to free the occluded air, and the pipette was then suspended on the hook provided.

All pipettes were then read at the end of one hour, accurately timed by a Smith stop-clock and a watch. The distance was then measured in millimetres from the bottom of the surface meniscus to the top of the red-cell columns, or to the upper surface of the buffy coat, or, as Westergren puts it, "to where the complete density appears to begin."

No adjustment for change of environmental temperature as recommended by Goldberg was made, but the effect of varying temperatures on the E.S.R. levels was noted throughout; indeed, no effect was found over the first eight hours of storage within the range 15–23° C. Beyond eight hours a rise in temperature, in particular, increased the error associated with storage.

Most of these experimental results were obtained with the pipettes suspended as described, and it was necessary to determine whether this practice was in itself liable to any major errors, of which the main one was thought to be the possibility of a lateral swinging movement of the suspended pipette as a result of draughts and other laboratory hazards.

This point was checked by running parallel experiments on one series of tubes hanging statically for the hour (static tubes), and on another series in which each tube was given a pendular movement over at least a

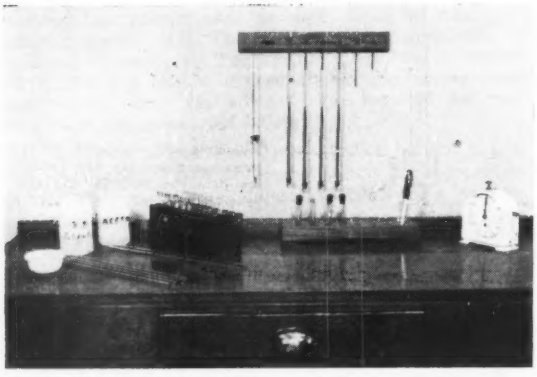

FIG. 4.—Wall-bracket for the Westergren pipette, used in a ward.

4-in. (10-cm.) arc by a sharp lateral blow, and the tube then allowed to swing until central once more (swinging tubes); this blow was repeated every 15 minutes during the hour, thus providing a degree of lateral movement that is more than could be reasonably expected under normal laboratory conditions. The results were virtually the same in the paralleled and duplicated sets of tubes.

It was thought that the blood diluent might just as well be normal saline as 3.8% sodium citrate solution, and this was then investigated, using parallel blood samples from two similar groups of patients. One line of duplicated samples was anticoagulated with sequestrene, then diluted with normal saline, while the other duplicated line was anticoagulated with sequestrene and then diluted with 3.8% citrate solution.

Results

The results of the various experiments are shown graphically. Figs. 5–11 show the comparison of methods on parallel blood samples with variables stated on each axis. The fixed line drawn in each case represents the 45 degrees line—that is, the line upon which the points should fall if the methods on the two axes gave identical results. Oxalated blood diluted with citrate was used as the reference standard throughout.

The results obtained when comparing normal saline with 3.8% sodium citrate as a diluent for the anticoagulated blood are not shown graphically, but tabulated data at the end of the statistical section (Nos. 8–10) show that there is no practical difference.

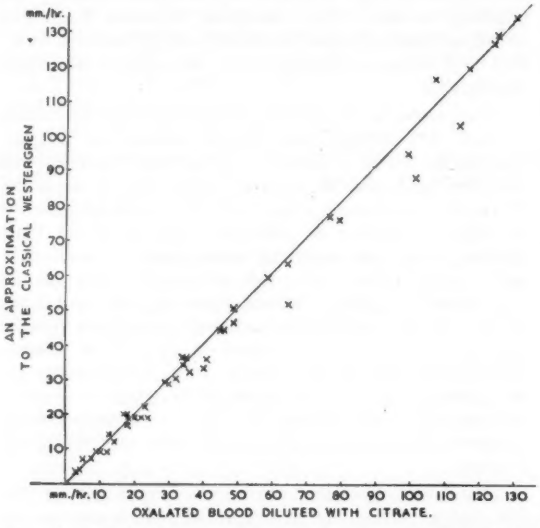

FIG. 5.—Relationship between a close approximation of the "classical" Westergren method and the oxalate method adopted as a standard reference. The slight scatter was thought to be due to the differences between readings of the syringe and 2-ml. pipette markings.

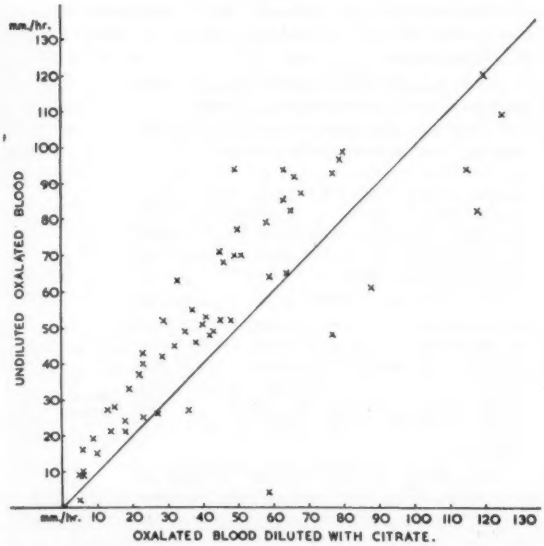

FIG. 6.—Shows the increased scatter when undiluted oxalated blood is used.

Statistics

The statistical analysis of the results obtained is as follows: R = The correlation coefficient. (N.B. 1.0 would equal complete correlation.) Ru and Rl = The estimated upper and lower confidence limits to the correlation coefficient. (N.B. These represent the limits within which the true value might be expected to lie, using the number of estimations at our disposal.)

1. An approximation to the classical Westergren *v.* oxalated blood diluted with citrate (46 estimations).
   R = 0.994644 Ru = 0.99728 Rl = 0.98987
2. Undiluted oxalated blood *v.* oxalated blood diluted with citrate (59 estimations).
   R = 0.844083 Ru = 0.9069 Rl = 0.7487
3. Undiluted sequestrenized blood *v.* oxalated blood diluted with citrate (113 estimations).
   R = 0.8205167 Ru = 0.8741 Rl = 0.7487
4. Sequestrenized blood diluted with citrate *v.* oxalated blood diluted with citrate (132 estimations).
   R = 0.9988845 Ru = 0.999 Rl = 0.99818
5. Sequestrenized blood diluted with citrate *v.* sequestrenized blood diluted with citrate (105 estimations).
   R = 0.9992154 Ru = 0.99945 Rl = 0.99878
6. Undiluted sequestrenized blood *v.* undiluted sequestrenized blood (92 estimations).
   R = 0.896117 Ru = 0.9302 Rl = 0.8456
7. Suspended and static sequestrenized blood diluted with citrate *v.* sequestrenized blood diluted with citrate suspended and swinging (108 estimations).
   R = 0.999133 Ru = 0.99945 Rl = 0.99878
8. Sequestrene blood with saline *v.* sequestrene blood with saline (87 estimations).
   R = 0.9986601 Ru = 0.99918 Rl = 0.99777
9. Sequestrene blood with citrate *v.* sequestrene blood with citrate (87 estimations).
   R = 0.9991699 Ru = 0.99945 Rl = 0.99878
10. Sequestrene blood with 3.8% sodium citrate *v.* sequestrene blood with normal saline (174 estimations).
    R = 0.994476 Ru = 0.99595 Rl = 0.99248

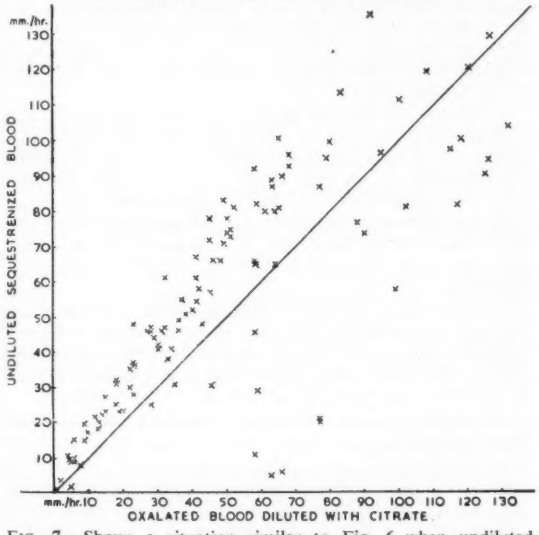

FIG. 7.—Shows a situation similar to Fig. 6 when undiluted sequestrenized blood is used.

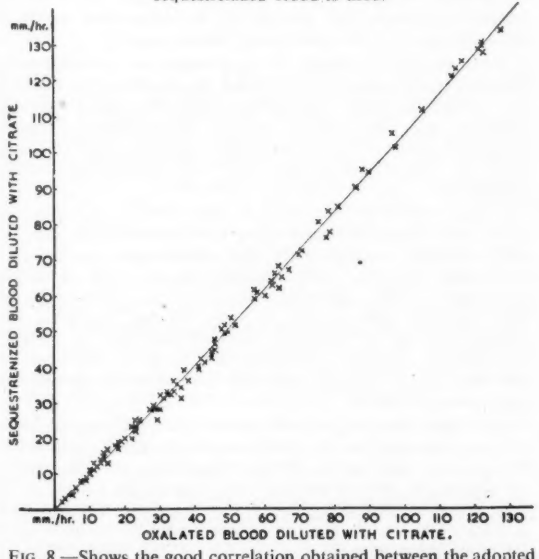

FIG. 8.—Shows the good correlation obtained between the adopted method using sequestrenized blood diluted with citrate and the standard reference method, and therefore, both with the adaptation of the classical method of Fig. 5 and, on the evidence of Goldberg's paper, with the true classical method.

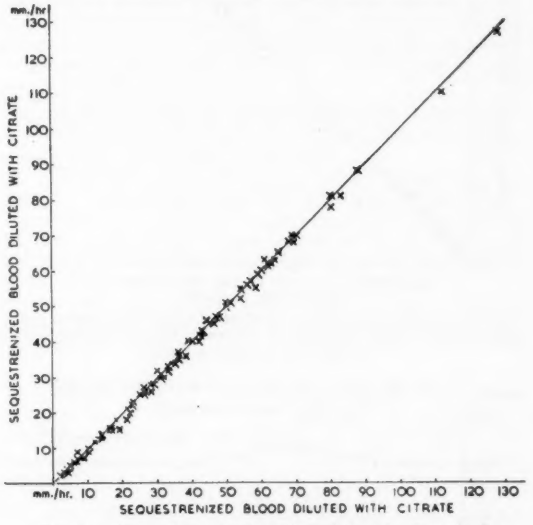

FIG. 9.—Shows the reproducibility of the Fig. 8 method.

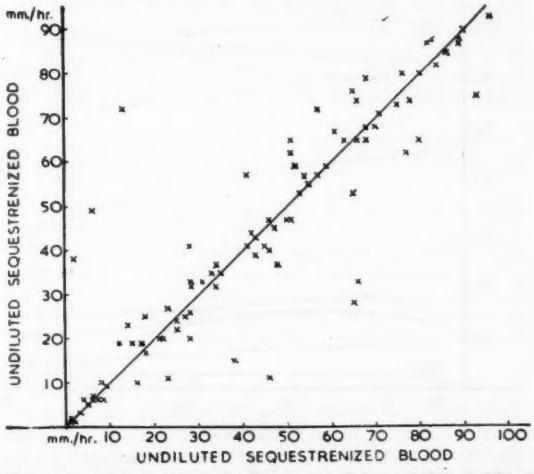

FIG. 10.—Shows the unreliability of using undiluted blood samples; for, with both axes varying, the wide scatter obtained cannot be correlated. Nevertheless, the degree of scatter is impressive.

Conclusions

It was concluded that the best method of determining the E.S.R. is to dilute 2 ml. of a sequestrenized blood sample with one-quarter its volume of isotonic 3.8% sodium citrate and then to examine the "fall" in a freely suspended tube. This conclusion was based on a comparison of E.S.R. values obtained using various methods against a common standard method in which oxalated blood diluted with one-quarter its volume of 3.8% sodium citrate solution was used. The adopted sequestrenized method and the standard method gave virtually identical results, and consequently, if the paper by Goldberg and Conway (1952) comparing the classical Westergren method with this so-called modified classical Westergren method is accepted as reliable, the results can be satisfactorily correlated with Westergren's classical standards, the ones in everyday use.

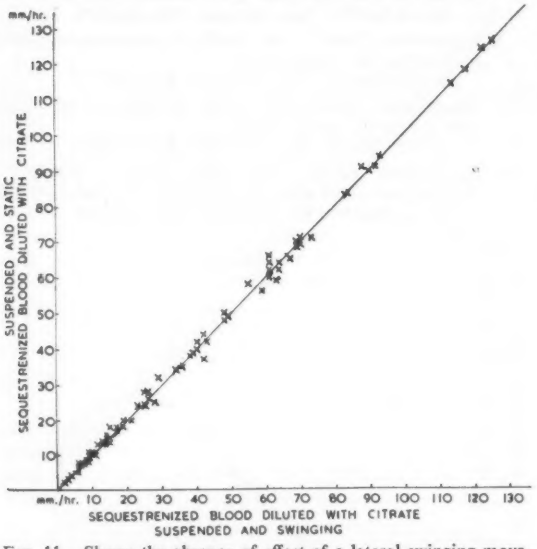
mm./hr.
SUSPENDED AND STATIC SEQUESTRENIZED BLOOD DILUTED WITH CITRATE
mm./hr. 10 20 30 40 50 60 70 80 90 100 110 120 130
SEQUESTRENIZED BLOOD DILUTED WITH CITRATE SUSPENDED AND SWINGING

FIG. 11.—Shows the absence of effect of a lateral swinging movement on the tube as described in the text. This was an interesting and perhaps surprising result.

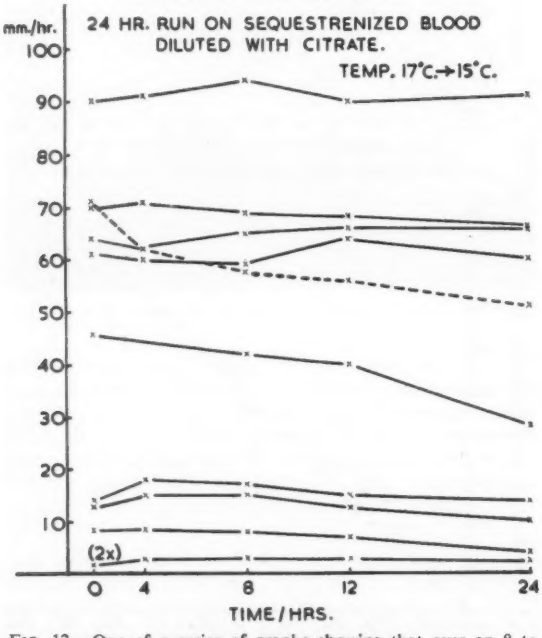

FIG. 12.—One of a series of graphs showing that over an 8 to 12-hour storage period the changes observed in the E.S.R. value are clinically insignificant, but that, on the whole, the rate of fall tends to lessen as the sample becomes older. (N.B.—Each line represents one blood sample followed under the stated conditions.)

It was also concluded that:

1. The method of using whole anticoagulated blood in a Westergren pipette is inaccurate, and, whilst admitting that the extra step of dilution is a time-consuming addition, it is one that is fully justified, as the values obtained when using undiluted blood are not reliable or repeatable, and E.S.R. estimations on parallel blood samples may often differ by as much as 20 mm. from patients with mild clinical symptoms. In particular patients, especially those showing major changes in blood-protein values, the differences may be much greater; one blood sample observed in this series produced parallel values of 6 and 49, and still greater differences have been noted in patients outside this particular set of experiments.

2. Upon consideration of the preceding paragraph, it is obvious that the use of undiluted anticoagulated blood makes an E.S.R. result of little value as a diagnostic screening aid in an out-patient clinic or when an inter-laboratory comparison of results is being made.

3. The methods using anticoagulated undiluted blood have never been standardized, and it is unjustifiable to assume that they have the same normal values as the "classical" method.

4. It has been shown on physico-chemical grounds and the evidence published that it is incorrect to use undiluted blood to study a phenomenon of this kind in a tube whose bore is less than 4 mm. (Westergren and Wintrobe pipettes in general use have a bore about 2.2 mm.–2.6 mm.).

We chose sequestrene as the standard anticoagulant for the following reasons:

1. It was already in use in our laboratory as a dry and adhering solid prepared in glass Wintrobe tubes for storing 3-ml. blood samples for routine investigations. (N.B.—This volume, 3 ml., is to be increased to 4 ml. in our laboratory to enable repeat tests to be carried out on samples producing anomalous results, or to allow for mishaps occurring during the laboratory investigations.)

2. It enables platelets to be counted on venepuncture blood, and red cells to be counted by an electronic counter—a situation quite impossible with the older oxalate mixture, as the counter cannot discriminate between insoluble calcium oxalate crystals and cells, the resulting error of this being in the order of millions per cubic millimetre.

3. The overall deterioration of such blood samples is less than with other anticoagulants, and especially is this so with reference to cell nuclei and membranes of markedly abnormal "bloods" when morphology is often of prime importance. This aspect of reduced deterioration of blood samples with time is also a very relevant factor if the hospital service is providing external facilities for general practitioners, who, by the nature of their work, often cannot get their blood samples into the laboratory as quickly as can a hospital ward.

4. Within the temperature range 15–23° C., a specimen of sequestrenized blood yields an acurate E.S.R. estimation for at least eight hours after venepuncture, though, ideally of course, the shorter the time that elapses the better. It is felt, however, that thereafter a stored sample tends to give a falsely low result, but this is not markedly so until after 24 hours have elapsed.

5. There is a high degree of repeatability of results.

6. Two minor points of more scientific than clinical import in the use of sequestrene are (*a*) a shortened phase 1,

and (*b*) a reduced tendency for cells to shrink, thereby increasing the accuracy of both the E.S.R. and the packed cell volume.

Sequestrene acts as an anticoagulant by chelating the calcium ions of the blood, through the action of its carboxyl (COOH) groups to form a soluble non-ionized salt. It is used in a concentration of 1–1.5 mg./ml. of blood, and it is suggested that if the higher figure is employed the chance of clotting occurring in the presence of inadequate mixing of blood and sequestrene is minimized, and it also permits a wider degree of error in measuring the 3 ml. of blood—a practical point in a busy ward.

Sequestrene is available as the di-potassium or the di-sodium salt, the solubilities in water being 20% W/V and 6% W/V respectively. We therefore chose to use the di-potassium salt as a 5% aqueous solution. The crystalline salt for preparing this solution can be obtained from the General and Pharmaceutical Co. Ltd., Judex Works, Sudbury, Middlesex.

Unfortunately, to prepare the 5% solution takes some two hours, owing to its slow solubility, and, likewise, the time taken to evaporate the solution to dryness in the Wintrobe tube at room temperature takes about five days, but this last procedure must be quite complete or a curious hygroscopic phenomenon occurs and the crystals liquefy once more. However, drying can be accelerated by the use of judicious heating (45° C. in an *x*-ray drying cupboard for two days) without any apparent deleterious effect on the anticoagulant properties of the chemical, a result which both the manufacturers and our chemistry department colleagues confirmed.

If excessive heat is used to dry the sequestrene a greater amount of the water of crystallization will be driven off, and this causes a tendency to form a fused "button" in the bottom of the tube, resulting in a reduced surface area of contact, and thereby necessitating greater care in the initial mixing of the anticoagulant and blood.

The Westergren pipette was chosen because: (*a*) it is in wide general use, (*b*) it requires only about 1 ml. of blood, and (*c*) its size makes it easy and practicable to use. The only other serious alternative, the Wintrobe pipette (100 mm. long), has, because of its small bore, been fully discredited in the literature, and, in spite of the convenience of being able to follow an E.S.R. estimation with a P.C.V. in the same tube, it should not be used.

When a Westergren pipette was made to deviate from the vertical in our experiments, a very real experimental error was introduced. This finding was fully supported by (*a*) similar findings in the available literature, and (*b*) the marked difference in the standard values as found by the rapid method of E.S.R. determination using a fixed angle tube as compared with a static vertical tube. These points suggested very strongly to us that the adoption of a freely suspended, and thus vertical, pipette would be a considerable advance.

This was achieved as described above, and the only novel variant thereby introduced that could not affect the static tube customarily used was the possibility of lateral movement caused by draughts and the like. In fact, quite strong draughts do not move the pipettes at all, but it was felt necessary to see if lateral movements would affect the value of an E.S.R. reading.

The adoption of the suspended Westergren pipette provides a method which is readily adaptable to most situations, from a large central laboratory to a small back room, and is cheaper, simpler to use, and easier to read than the conventional method.

Other facts noted during this series of experiments were:

1. Relatively dirty pipettes—that is, those merely washed in tap-water and allowed to dry—did not seem to affect the accuracy of the readings to any great degree, an observation of importance for a busy ward, where chemical cleaning of tubes is not always practicable.

2. Varying the blood/anticoagulant dilutions had a relatively marked effect on the E.S.R. and hence the 1 in 4 dilution should be carefully made, using, if possible, microburettes and accurate pipettes.

3. Contamination with spirit, etc., at any stage in the process from venepuncture to estimation must be prevented.

4. A few bubbles in the Westergren pipette seem to have very little effect on the E.S.R. itself, provided they are present at the top of the blood column or remain static at the bottom. Should they be present at the top of the blood column, their volume must be deducted in reading the E.S.R., as they, in themselves, do not form a part of the fluid column.

5. The estimation of the E.S.R., using general hospital syringe service syringes and done in a central haematological laboratory, appears to benefit in that it becomes more repeatable and at the same time relieves the houseman of humdrum work he need not be required to perform.

6. Westergren's "classical" method is not as accurate as the modified classical method of Goldberg, because in the latter: (*a*) the error introduced by immovable bubbles in the syringe is avoided, and (*b*) the 2-ml. pipette used as described for diluting blood is more accurately read than the plunger mark of a glass syringe.

7. The ability to pick up the suspended Westergren pipette from its hook greatly reduces the breakage rate of pipettes, and facilitates the reading of the result.

8. The general practice of cleaning glass pipettes using the sequence water–alcohol–ether–air, in contrast to water–acetone–air, was found to be unnecessary for the following reasons: (*a*) it is much more expensive, (*b*) it requires an extra container for the fluids, and (*c*) the amount of inflammable vapour which reaches the room and the drain is greater with alcohol–ether than with acetone. (N.B.—Neither sequence affects the E.S.R., and acetone is fully miscible with water.)

Considerations

From a review of the literature and supported by these experimental results, a series of concepts was deduced for guidance in interpreting an E.S.R. value.

1. That Westergren's original normal E.S.R. ranges (normal male adult, 0–5 mm. per hour; normal female adult, 0–10 mm. per hour) were felt to be too narrow, and that a further 5 mm. should be added to each. Within these ranges low readings—that is, 1 mm. and 2 mm.—are abnormal.

2. That in adults over 50 years, higher values may be normal.

3. That in pregnancy, which normally causes a marked rise in E.S.R., the normal range should be up to 45 mm. in one hour.

4. That normal neonates have a low E.S.R.—about 2 mm.—by the standard method.

N.B.—The micromethod of determining the E.S.R. of an infant, using a capillary tube and blood obtained by heel stab, is relatively inaccurate, and where an abnormal value is obtained (based on locally accepted norms) the estimation should be repeated by the suggested standard method.

The normal E.S.R. range in use at any particular centre will be modified by local conditions. The adult West African, in a centre using heparin as anticoagulant for the blood samples, is credited with having a normal range of 5 to 30 mm. per hour. This may possibly be due to masked endemic disease, in addition to the effects of the heparin.

Summary

The various methods of estimating the E.S.R. employed in the Edinburgh group of hospitals have been investigated and found wanting. A new method has been suggested, employing sequestrene as the anti-coagulant and using a suspended Westergren pipette in place of the static pipette usually employed. This new method has been checked and found satisfactory, and has been in use over the past 18 months in the Royal Infirmary, Edinburgh.

It is with great pleasure that I acknowledge the help and advice of so many people—in particular, Sir Stanley Davidson, my recent chief; Dr. J. Richmond; Dr. A. Doig and other senior members of his staff; Mr. Sklaroff, statistician at the Usher Institute; Mr. R. Samson and Miss F. McNulty, laboratory technicians; and the secretaries, Misses Williams, Potts, and Webster, and other members of the unit.

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ORTHO-CRESOTINATE AND DIABETES MELLITUS

BY

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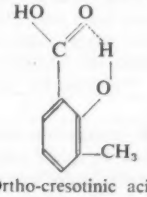
Aspirin in full therapeutic doses relieves mild diabetic symptoms, lowers the fasting blood-sugar level, and reduces glycosuria and ketonuria in patients with mild to moderately severe diabetes mellitus (Reid, Macdougall, and Andrews, 1957). One of the disadvantages of aspirin therapy, however, is the fairly frequent occurrence of undesirable side-effects, such as tinnitus and deafness, with the high dosage of the drug required to achieve satisfactory control of the diabetes.



Ortho-cresotinic acid.

Stockman (1912) observed that sodium ortho-cresotinate (see Formula) was as effective as sodium salicylate in treatment of rheumatic fever, but even with high dosage it did not cause deafness or tinnitus. The effect of ortho-cresotinate in diabetes mellitus has been investigated to find out whether it has a similar hypoglycaemic action to that of salicylate without its undesirable side-effects.

Nine patients with diabetes mellitus were treated with ortho-cresotinate, and clinical particulars are shown in Tables I and II.

TABLE I.—*Clinical Particulars of Group* 1. *Patients Previously Treated by Dietary Restriction Alone*

Case No.	Age	Sex	Weight (kg.)	Duration of Diabetes	In-patient Diet	
					g. Carb./Day	Total Cals./Day
1	68	F	57·7	3 years	150	1,600
2	59	F	72·9	1 month	120	1,300
3	60	F	71·5	8 years	150	1,500
4	57	F	56·5	2 ,,	150	1,700
5	68	F	52·9	3 months	150	1,700
6	55	M	59·5	3 ,,	148	1,600

TABLE II.—*Clinical Particulars of Group* 2. *Patients Previously Treated by Diet and Insulin*

Case No.	Age	Sex	Weight (kg.)	Duration of Diabetes	Diet		Insulin Requirement (Units/Day at End of Control Period)
					g. Carb./Day	Total Cals./Day	
7	49	F	56·5	1 year	195	2,100	28 I.Z.S.
8	49	F	50·7	10 years	195	2,100	50 ,,
9	37	M	79·9	6 ,,	200	2,000	54 ,,

The first group of six patients (group 1) had been treated previously by dietary restriction only for periods varying from one month to eight years, but control of the diabetes had not been satisfactory, as indicated by the occurrence of mild diabetic symptoms in five of the patients, and the presence of persistent glycosuria and elevated blood-sugar levels in every patient. Two patients (Cases 2 and 3) were overweight at the beginning of the investigation; the other four were at or below their optimum weight. The second group of three patients (group 2) had already been treated by diet and insulin before the investigation. Their insulin requirement when admitted to hospital ranged from 28 to 88 units of insulin zinc suspension (I.Z.S.) daily.

Methods of Investigation

All patients were admitted and detained in hospital for the duration of the investigation. Treatment was controlled and the effect of the drug determined by frequent estimations of the fasting blood-sugar and serum ortho-cresotinate levels and daily measurement of sugar and ketone output in 24-hour urine. Every patient in group 1 was first treated by dietary restriction until the fasting blood-sugar was stable. This control period varied from 7 to 13 days. The daily carbohydrate intake, ranging from 120 to 150 g. was kept constant throughout both the control and treatment periods. The diet contained 65 to 79 g. of protein, and 65 to 85 g. of fat, and the total calorie content ranged from 1,300 to 1,700 a day. At the end of the control period of dietary restriction the patients were given a course of ortho-cresotinate which lasted for at least two to three weeks.

The three patients in group 2 were treated initially by dietary restriction and insulin for a control period of 10 to 24 days. During this time the daily dosage of insulin was altered if necessary to stabilize the fasting blood-sugar. After the control period a course of ortho-cresotinate, lasting for two to three weeks, was started and insulin administrations continued. The dose of

insulin was then gradually reduced, if indicated, by a reduction in fasting blood-sugar and glycosuria. In this way the amount of insulin replaced by the course of the drug was determined for each patient.

The diets which the three patients requiring insulin had taken as out-patients were continued in two, but in the remaining patient the daily carbohydrate intake was reduced from 287 to 200 g. Throughout the investigation the diets were constant in carbohydrate content, which ranged from 195 to 200 g. daily, with total calorie content of 2,000 to 2,100 calories a day: the protein and fat contents ranged from 85 to 93 g. for protein and 92 to 123 g. for fat each day.

The drug was given as a solution of sodium ortho-cresotinate to one patient and as acetyl-ortho-cresotinate in the form of tablets to the others. In all cases it was given four-hourly during the day, omitting one dose in the middle of the night. Actual dosage, which ranged from 1 to 1.3 g. four-hourly, was controlled by frequent estimations of serum ortho-cresotinate level (Trinder, 1954) to maintain a serum level of 30 to 35 mg./100 ml. The doses of the drug required and the mean serum ortho-cresotinate level for individual patients, which varied from 27 to 40 mg./100 ml., are shown in Table III.

TABLE III.—*Dose of Ortho-cresotinate and Serum Ortho-cresotinate Level*

Case No.	Weight (kg.)	Maintenance Dose (g. given 5 Times/Day)	Serum Ortho-cresotinate Level (mg./100 ml.)	
			Range	Mean
1	57·7	1·0	25–28	27
2	72·9	1·0	29–34	32
3	71·5	1·0	26–38	34
4	56·5	1·2	28–35	32
*5	52·9	1·2	32–39	35
6	59·5	1·0	27–41	35
7	56·5	1·3	36–46	40
8	50·7	1·2	31–48	40
9	79·9	1·3	35–45	40

* This patient was treated with sodium ortho-cresotinate; all others with acetyl-ortho-cresotinate.

Response to Ortho-cresotinate

The response to treatment of the six patients in group 1 is considered first and results are presented in Tables IV, V, and VI.

Symptoms.—When admitted, five of the six patients treated by dietary restriction alone complained of mild diabetic symptoms, five complained of nocturia, two of thirst, one of pruritus vulvae, and one of polyuria; the other patient was symptom-free. By the end of the control period of dietary restriction three patients had become symptom-free, and by the end of the course of ortho-cresotinate all patients were symptom-free, with the exception of one who still complained of thirst and polyuria. This patient continued to produce large volumes of urine of low specific gravity, though the fasting blood-sugar level was normal and there was no glycosuria.

Fasting Blood Sugar.—Fasting blood-sugar levels were estimated three to four times a week by Lehmann and Silk's (1952) modification of Folin and Wu's method. At the end of the dietary control period all six patients still showed stable and elevated fasting blood-sugar level. A reduction in fasting blood-sugar level was noted in every patient during the course of ortho-cresotinate—the level falling to within normal limits in five patients and to 145 mg./100 ml. in the sixth patient by the 14th and 15th day of treatment.

The mean value for the fasting blood sugar in the six patients fell from 208 mg./100 ml. on the day of starting the course to 114 mg./100 ml. by the 14th to 15th day of treatment. The significance of the difference between the means was determined by Student's t-test. The fall in blood sugar by the 14th to 15th day of treatment was found to be highly significant ($P<0.001$). The fasting blood-sugar levels during the last three to four days of control period and during the period of treatment are shown in Table IV.

TABLE IV.—*Effect of Ortho-cresotinate on Fasting Blood-sugar Level of Patients Previously Treated by Dietary Restriction Alone*

Case No.	Fasting Blood Sugar (mg./100 ml.)				
	Before Ortho-cresotinate		During Ortho-cresotinate		
	Day 3–4	Day 0–1	Day 3–4	Day 7–8	Day 14–15
1	200	193	152	126	117
2	193	215	228	138	109
3	204	234	148	163	145
4	183	165	110	121	95
5	237	233	145	147	115
6	186	208	128	111	105
Mean ..	201	208	152	134	114

Glycosuria.—The total urinary sugar output in 24 hours was estimated daily throughout the period of investigation by Benedict's (1911) method and the results were expressed in g. of glucose per 24 hours. Glycosuria was present in five of the six patients by the end of the control period. The only patient not showing glycosuria by that time was one who had already had a short course of cresotinate of seven days' duration, which had to be discontinued because of side-effects, the drug being restarted five days later. During the period of treatment with ortho-cresotinate there was a reduction in glycosuria in five cases and the urine became sugar-free in four patients. The other two patients still showed a small amount of reducing substance in the urine. The mean value for 24-hour urine-sugar output fell from 19.8 g./24 hours at the start of treatment to 2.5 g./24 hours on the 14th to 15th day of treatment. This small quantity of reducing substance may be accounted for by excretory products of ortho-cresotinate in the urine which reduce Benedict's solution. For the five patients who still showed glycosuria at the end of the control period the significance of the difference between the means was determined by Student's t-test. The fall in glycosuria by the 14th to 15th day of treatment was found to be just significant ($P>0.02$ but <0.05). The results for individual patients are shown in Table V.

TABLE V.—*Effect of Ortho-cresotinate on Glycosuria*

Case No.	Total Urine Sugar (g./24 Hrs.)				
	Before Ortho-cresotinate		During Ortho-cresotinate		
	Day 3–4	Day 0–1	Day 3–4	Day 7–8	Day 14–15
1	16	19	0	0	12·0
2	26	40	14	1	0
3	46	41	10	6	0
4	18	0	0	13	0
5	11	12	10	2	3
6	10	7	0	0	0
Mean ..	21·2	19·8	5·7	3·7	2·5

Ketonuria.—Ketones in the urine were estimated by the method of Greenberg and Lester (1944). The urine ketones were measured quantitatively only if the urine gave a positive result to Rothera's test. Only two patients had ketones present in the urine on admission, and in both cases the ketonuria disappeared during the

control period. Slight ketonuria occurred in one patient during the course of ortho-cresotinate but lasted for only one day.

Oral Glucose-tolerance Tests.—Oral glucose-tolerance tests were carried out on all six patients during the control period just before treatment was started and again on the 13th to 14th day of the course of ortho-cresotinate. 50 g. of glucose was given orally with the patients fasting, and the blood-sugar levels were estimated when fasting and at ½, 1, 1½, and 2 hours after administration of the glucose. The results of these tests are shown in Table VI. The blood-sugar curves on the 13th to 14th day of the course of ortho-cresotinate were all similar but at a lower level than those obtained before treatment was started.

TABLE VI.—*Oral Glucose-tolerance Test—50 g. Glucose (Orally When Fasting)*

Case No.	Blood Sugar (mg./100 ml.) After Glucose									
	Fasting		½ Hour		1 Hour		1½ Hours		2 Hours	
	Pre-Cres.	Day 13–14	Pre-Cres.	Day 13–14	Pre-Cres.	Day 13–14	Pre-Cres.	Day 13–14	Pre-Cres.	Day 13–14
1	193	117	222	228	281	228	333	242	333	255
2	215	109	254	175	330	196	339	214	339	182
3	234	145	333	220	337	280	382	280	371	212
4	165	95	270	237	—	237	310	244	310	244
5	233	137	378	237	356	259	356	208	311	185
6	208	105	254	168	346	217	362	246	330	224
Mean	208	118	285	211	330	236	347	239	332	217

The response to the drug of the three patients in group 2 who required insulin is now considered.

Case 7

A woman aged 49, with diabetes of one year's duration, remained well stabilized and controlled while receiving 195 g. of carbohydrate and a dose of 28 units of I.Z.S. daily. During ortho-cresotinate therapy the dose of insulin was reduced over a period of five days and then discontinued altogether, the diabetes remaining just as well controlled by ortho-cresotinate alone as by insulin therapy when judged by fasting blood-sugar levels. The fasting blood-sugar remained within normal limits throughout the period that ortho-cresotinate treatment replaced insulin therapy. Glycosuria, which was slight and intermittent during the control period with insulin, showed a slight increase during cresotinate therapy. There was no ketonuria during the control or treatment periods. The oral glucose-tolerance test when the patient was receiving insulin alone and then on ortho-cresotinate alone showed similar curves, but the level was slightly lower during ortho-cresotinate therapy. In this patient 28 units of I.Z.S. was replaced by ortho-cresotinate therapy, and the diabetes was satisfactorily controlled.

Case 8

A woman aged 49, who had had diabetes for 10 years, had also suffered from rheumatoid arthritis for the past three years, and this was active when she was admitted. Her diabetes had not been well controlled as an out-patient, as shown by symptoms of increased frequency of micturition, nocturia, and considerable glycosuria. Her insulin requirement as an out-patient had been 16 units of I.Z.S. (amorphous) and 72 units of I.Z.S. daily, but by the end of the control period the insulin requirement had fallen to 50 units of I.Z.S. daily, presumably owing to stricter dietary control while in hospital. Marked fluctuation in fasting blood-sugar level with considerable variation in degree of glycosuria continued through the control period and indicated an unstable state of diabetes mellitus.

During ortho-cresotinate therapy the dose of insulin was reduced to 12 units of I.Z.S. (amorphous) plus 32 units of I.Z.S. daily, and after cresotinate had been discontinued the insulin requirement was in the range of 12 units of I.Z.S. (amorphous) plus 52 units of I.Z.S. to 16 units of I.Z.S. (amorphous) plus 56 units of I.Z.S. daily. The fall in insulin requirement during cresotinate treatment was slight, amounting to 20 units of I.Z.S. daily, but the fluctuation in fasting blood-sugar and glycosuria was just as pronounced during combined insulin and cresotinate treatment as with insulin alone.

Case 9

A man of 37 had suffered from diabetes mellitus for six years. His diabetes had not been well controlled during the six months prior to admission and he had experienced frequent hypoglycaemic attacks, often without any warning. As an out-patient he had taken a diet of 287 g. of carbohydrate daily, with an insulin dosage of 88 to 92 units of I.Z.S. daily. After admission to hospital the diet was reduced to 200 g. of carbohydrate, with a total of 2,000 calories, and this was then strictly adhered to throughout the control and drug-treatment periods.

During the control period further hypoglycaemic attacks were experienced and the dose of insulin was reduced to 54 units of I.Z.S. daily. Marked fluctuations in fasting blood-sugar level and degree of glycosuria occurred and there was intermittent ketonuria throughout the control period.

During ortho-cresotinate therapy the insulin dose was reduced and he was stabilized by 28 to 36 units of I.Z.S. daily. His insulin requirement thus fell by about 18 units of I.Z.S. daily during the course of ortho-cresotinate. Though considerable variations in fasting blood-sugar, glycosuria, and ketonuria continued during the course of cresotinate, no actual hypoglycaemic symptoms were experienced during combined drug-insulin therapy. Combined insulin and ortho-cresotinate therapy was continued as an out-patient, and he has been working regularly for a year. During this time he has experienced only occasional hypoglycaemic symptoms, and he now also gets adequate warning of attacks. The striking point about this patient was not so much the amount of insulin replaced by ortho-cresotinate as the virtual elimination of troublesome hypoglycaemic attacks. Undoubtedly combined insulin and ortho-cresotinate therapy was more satisfactory than treatment with insulin alone.

Incidence of Side-effects

Of the nine patients treated with ortho-cresotinate, seven experienced side-effects from the drug. The most common symptoms were anorexia, nausea, headache, and vomiting. These symptoms occurred mainly during the first week of the course (2nd to 8th day) and then tended to pass off. Two patients had symptoms of headache, dizziness, anorexia, nausea, and vomiting severe enough to cause temporary discontinuance of the drug, and relief of these symptoms occurred within one to two days. When treatment was restarted a few days later a full 14-days course of the drug was given. During this second course only slight temporary headache was experienced by one patient, and the other remained symptom-free. Smaller doses of the drug were given at the beginning of the second course, and this resulted in a slower rise in the serum ortho-cresotinate level. These symptoms were due to overdosage with the drug and were associated with high serum ortho-cresotinate levels. They occurred especially in patients when there was a rapid initial rise in serum ortho-cresotinate level and could be avoided by a more gradual build-up of the serum concentration of the drug. The toxic effects were all temporary except for persistent anorexia in one patient when the serum level was 40 mg./100 ml. Side-effects occurred mainly when the serum ortho-cresotinate levels were 35 mg./100 ml. or over, though in some

patients they occurred at as low a level as 32 mg./100 ml., and other patients were symptom-free at levels of 40 to 45 mg./100 ml.

The outstanding feature about these results was the complete absence of deafness or tinnitus in every patient during treatment with ortho-cresotinate.

Body Weight.—Weight changes during the control period ranged from a gain of 0.7 kg. to a loss of 3.7 kg. During treatment with ortho-cresotinate two patients showed a slight increase in weight and the others lost from 0.4 to 4.6 kg. It was the patient whose diet was reduced from 287 to 200 g. of carbohydrate daily who lost 4.6 kg.

Discussion

These results show that ortho-cresotinate has a similar hypoglycaemic action to aspirin in diabetes mellitus. A disadvantage of aspirin therapy in diabetes mellitus is the fairly frequent occurrence of side-effects with the high dose of the drug required to cause a maximum hypoglycaemic effect. The annoying symptoms of deafness and tinnitus often occur during treatment with aspirin, but neither of these symptoms was experienced by any of the patients treated with ortho-cresotinate.

The drug was given with the aim of attaining a serum cresotinate level of 30 to 40 mg./100 ml. and the serum levels during the course were in the range of 27 to 40 mg./100 ml. for individual patients. With these doses there was a high incidence of temporary side-effects from the drug, the most common being headache (3 patients), anorexia (4 patients), nausea (5 patients), vomiting (3 patients), dizziness (3 patients, and drowsiness (1 patient). These side-effects were due to overdosage, and their occurrence indicates that ortho-cresotinate therapy, like aspirin, requires to be controlled initially by estimations of serum level of the drug until a suitable dose has been determined for each patient. This is necessary because of the variation in the dose required by individual patients to attain the same serum level of the drug. This means that it is advisable to admit patients to hospital to start ortho-cresotinate therapy until the precise dose for each individual has been determined. A slow build-up of dose is recommended to prevent the development of undesirable side-effects.

Summary

The effect of ortho-cresotinate in diabetes mellitus has been investigated in nine patients by administering the drug for two to three weeks after an initial control period. In the six patients previously treated by diet alone a course of ortho-cresotinate relieved mild symptoms of diabetes and caused a fall in fasting blood-sugar and a reduction in glycosuria in all cases. During a course of the drug in the other three patients already being treated with insulin the insulin requirement of all three patients was reduced and in one patient 28 units of insulin zinc suspension daily was replaced by ortho-cresotinate therapy with satisfactory control of the diabetes.

No deafness or tinnitus was experienced by any of the patients, and the most frequent side-effects which occurred in seven patients were headache, anorexia, nausea, and vomiting. These were all temporary, and could be avoided by slowly increasing the dose until the required amounts for each individual patient had been reached.

Ortho-cresotinate has a similar hypoglycaemic effect to aspirin in patients with mild to moderately severe diabetes mellitus without the undesirable side-effects of deafness and tinnitus.

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TWO TYPES OF LUPUS ERYTHEMATOSUS CELL FACTOR, SHOWN BY INDUCED L.E. CELL PHENOMENON IN DOGS

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In a previous paper (Bencze, 1960) it was shown that typical lupus erythematosus (L.E.) cell formation can be induced in dogs by transfusion of systemic lupus erythematosus (S.L.E.) plasma. Similar investigations completed on hospital patients gave evidence of the existence of transferable and non-transferable L.E. plasma factors (Bencze, Kovács, and Cserháti, 1959).

The present communication reports on two types of L.E. plasma factor, as shown by the results of transfusing S.L.E. plasma in experiments on dogs. The experiments were done according to the technique described previously (Bencze, 1960).

Results

The plasma containing L.E. cells from nine patients with typical signs of S.L.E. was transfused into 17 dogs (Table I). The introduction of plasma from three S.L.E. patients produced the L.E. cell phenomenon in the dogs. On the other hand, plasma from six S.L.E. subjects failed to induce the L.E. cell phenomenon.

Further human and animal experiments were carried out with plasma containing L.E. cells from 11 donors (Table II). Plasma of six S.L.E. patients was transfused into human subjects as well as into dogs; plasma from five S.L.E. donors was transfused either into human subjects or dogs, but not both. The plasma from six S.L.E. patients gave identical results in man and dog. The transferable L.E. cell factor produced the L.E. cell phenomenon both in man and in dog (Table II, lines 1 and 2). In four cases the L.E. plasma factors proved

to be non-transferable, the results being negative in both man and dog (Table II, lines 3, 4, 5, 6).

Further investigations were made to find out whether the amount of transfused plasma was to be responsible for the presence of these two different types. These experiments were also carried out by the same technique. Plasma from six different donors (L.E. cell positive) was transfused into dogs in varying amounts. The doses of plasma according to the weight of the dogs were, respectively, 10, 2, 1, 0.5, 0.25, and 0.125 ml./kg., and so on (Table III).

In our previous experiments plasma from five different S.L.E. patients (L.E. cell positive), which proved to be not transferable, was transfused in doses of 10 ml./kg. into dogs: none of these specimens of plasma produced L.E. cells. Plasma from patient O. P., however, was found to carry the transferable L.E. cell factor, producing L.E. cells repeatedly at a dose of 0.125 ml./kg. No evidence of L.E. cells was found in the recipient when smaller quantities were transfused (Table III).

Discussion

Plasma taken from nine L.E. cell positive S.L.E. patients was transfused into dogs, but plasma from only three of these donors produced L.E. cells in the recipients: plasma from the other six donors gave negative results. The S.L.E. plasma transfer experiments in dogs confirmed the results obtained in our previous experiments completed on man, which showed the existence of two types of L.E. cell factor. We arrived at identical results both in human subjects and in dogs: the transferable L.E. cell factor proved to be transferable in man and dog, and vice versa.

Our further experiments gave evidence that the existence of two types of L.E. cell factor is in no way related with the amount of transfused plasma. Experiments with plasma from six different S.L.E. donors were completed to find out whether the amount of transfused plasma was responsible for the production of two types of L.E. cell factor. Out of six S.L.E. subjects, the plasma of one patient (O. P.) proved to be transferable in both man and dog. The L.E. cell phenomenon was produced in this experiment by transfusing as small a dose as 0.125 ml./kg. in dogs. The transfusion of even 10 ml./kg. of non-transferable plasma of five S.L.E. patients failed to produce L.E. cells in dogs.

TABLE II.—*S.L.E. Plasma Transfer Experiment on Man and Dog (Comparative Table)*

S.L.E. Donor		Recipient	
No.	Initials	Man	Dog
1	O.P.	+	+
2	T.I.	+	+
3	P.J.	0	0
4	P.F.	0	0
5	V.M.	0	0
6	H.K.	0	0
7	A.J.	0	—
8	T.J.	0	—
9	K.E.	—	+
10	K.K.	—	0
11	S.M.	—	0

+ = L.E. cell. 0 = L.E. cell negative. — = No experiment.

TABLE I

S.L.E. Patient No.	Dog No.	Recipient Dog			S.L.E. Donor			Recipient (Days after Transfusion)								Transfusion Reaction
		Sex	Body Weight kg.	Blood Group	Name	Blood Group	Transfused Plasma ml.	2/24	6/24	1	2	4	6	8	10	
1	1	F	18	AB	K.E.	O	90	++	+	0	0	0	0	0	0	0
	2	M	12	AB	K.E.	O	60	+	+	+	+	0	0	0	0	0
2	3	F	13	B	O.P.	AB	60	++	+++	++	+	0	0	0	0	0
	4	M	12	B	O.P.	AB	60	+++	++++	++	++	0	0	0	0	0
	5	F	6·8	AB	O.P.	AB	30	++	++++	+						0
	6	M	9·0	AB	O.P.	AB	18	+	++++	+	+	+	0	0	0	0
3	7	F	21	B	T.I.	A	90	+	++++	++	++	+	+	0		0
	8	M	10	AB	T.I.	A	50	++++	++++	+++	++	++	+	+	0	0
4	9	M	7·8	AB	P.J.	O	30	0	0	0	0	0	0	0	0	0
	10	M	7	AB	P.J.	O	14	0	0	0	0	0	0	0	0	0
5	11	M	10·20	AB	P.F.	A	40	0	0	0	0	0	0	0	0	0
	12	F	11·0	AB	P.F.	A	22	0	0	0	0	0	0	0	0	0
6	13	F	11·20	AB	K.K.	A	46	0	0	0	0	0	0	0	0	0
	14	M	12	AB	K.K.	A	24	0	0	0	0	0	0	0	0	0
7	15	M	12·20	AB	S.M.	O	25	0	0	0	0	0	0	0	0	0
8	16	M	12·40	AB	V.M.	A	37	0	0	0	0	0	0	0	0	0
9	17	M	10	AB	H.K.	O	40	0	0	0	0	0	0	0	0	0

TABLE III

Dog No.	Recipient Dog			S.L.E. Donor		Transfused Plasma		Recipient (Days after Transfusion)								Transfusion Reaction
	Sex	Body Weight kg.	Blood Group	Initials	Blood Group	ml./kg.	Vol. given (ml.)	2/24	6/24	1	2	4	6	8	10	
1	M	8	AB	P.J.	O	10·0	80	0	0	0	0	0	0	0	0	0
2	M	10	AB	P.F.	A	10·0	100	0	0	0	0	0	0	0	0	0
3	F	9	AB	K.K.	A	10·0	90	0	0	0	0	0	0	0	0	0
4	M	12·40	AB	S.M.	O	10·0	125	0	0	0	0	0	0	0	0	0
5	M	8	AB	V.M.	A	10·0	80	0	0	0	0	0	0	0	0	0
6	M	9	AB	O.P.	AB	2·0	18	+	++++	0	0	0	0	0	0	0
7	M	10	AB	O.P.	AB	1·0	10	+	++++	0	0	0	0	0	0	0
8	M	12	AB	O.P.	AB	0·5	6·0	+	++++	0	0	0	0	0	0	0
9	M	11	AB	O.P.	AB	0·25	2·8	+	++	+	+	+	+	0	0	0
10	M	11	AB	O.P.	AB	0·125	1·4	++	++	+	+	+	0	0	0	0
11	M	10	AB	O.P.	AB	0·06	0·6	0	0	0	0	0	0	0	0	0
12	M	12	AB	O.P.	AB	0·03	0·36	0	0	0	0	0	0	0	0	0

Summary

Two types of L.E. cell factors—transferable and non-transferable—were found in experiments in which plasma from patients with systemic lupus erythematosus was transfused into dogs.

Identical results were obtained in human subjects and in dogs with transfusions of transferable and non-transferable L.E. plasma factor.

The amount of transfused L.E. plasma appears not to be responsible for the production of two types of L.E. cell factor.

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IS THERE A STEIN–LEVENTHAL SYNDROME?

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During the past twenty years much attention has been paid to the pathological findings in cases of multiple small cysts in ovaries with thickened capsules. Stein and Leventhal (1935) first described a group of cases with such findings and have recently reiterated their conception of what has become known as the Stein–Leventhal syndrome. Stein (1959) defines it as "sterility accompanied by secondary amenorrhoea, hirsuties in 50–75%, and consistently enlarged symmetrical ovaries with a definite pathological pattern." The ovarian changes, he says, may also be found in cases of the adrenogenital syndrome. Leventhal (1958) describes the ovarian pathological findings. The tunica is thick, tough, and pearly white. There are multiple small cysts. The follicles may or may not have layers of granulosa cells. The most consistent finding he describes is hyperplasia of the theca interna with frequent luteinization. The absence of corpora lutea or corpus luteum cysts is noted, and he states that when secretory endometrium is found there is again no evidence of corpora lutea, but marked luteinization of the theca

Present Investigation

The findings at Chelsea Hospital for Women have been quite different from any reported so far, and are therefore worthy of note.

The clinical features are correlated with the histological findings in two groups, while a third group acts as a control.

Group 1: Typical histology + clinical syndrome of infertility, irregular periods, and hirsutism.

Group 2: Typical histology + clinical syndrome and corpus luteum.

Group 3: Controls; patients in the same age-group, seen during the same period of time, but with varying indications for operation.

The main findings, histologically, are recorded in Table I. All the histological preparations which provide the material for this analysis were examined "blind," and no indication was given of the group to which the section belonged. It will be noted that histological changes in the ovarian capsule are not included in the table, and this is because we have not found it possible to decide a "normal" for each age, owing to the wide variation in the thickness of the capsule. The clinical features are recorded in Table II.

It will be seen that our findings approximate fairly closely as regards the large number of cystic follicles, while the operation notes mention the tough fibrous capsule. A layer of granulosa cells is present in all but one of our cases, but hyperplasia of the theca interna is not as evident as Leventhal has found. In fact, though the theca interna has been present, hyperplasia has not been noted in a single case (Table I).

Luteinization of the theca interna has not been a feature in the cases studied, though it is thought by Shippel (1955) and by Plate (1958) to constitute the principal finding. This hyperthecosis is reported as affecting the theca externa as well, but in our series no cases have come to light where the theca externa has shown hyperplasia. Leclerq (1958) in a series of 51 cases reports very similar findings to those of Leventhal, but we are unable to find the same degree of specificity described by them.

Ovulation has been reported by Stein *et al.* (1949) as occurring very rarely, at long intervals, or not at all; and Kaufman *et al.* (1959) refer to a characteristic lack of recent corpora lutea. Shippel mentions ovulation as a freak occurrence; Ingersoll (1955) says that all the patients are anovulatory, the only common finding being the ovarian pathology; while Prunty *et al.* (1958) also note the absence of ovulation in this syndrome. Bailey (1959) found no corpus luteum in 63 cases. The striking thing about our cases is the comparatively large number showing corpora lutea.

The question of ovulation is obviously of prime importance, since the object of treating these patients is to enable them to ovulate and thus become pregnant. The operation of wedge resection, detailed by Leventhal (1958), may produce regular menstruation in a patient who was previously ovulating with an irregular cycle. It is doubtful whether the operation is indicated in such cases.

Wedge resection may also produce normal ovulatory cycles in patients who were previously suffering from amenorrhoea. The continuance of normal cycles, with or without ovulation, is not necessarily permanent after the operation (Table II).

Groups 1 and 2 show the same features except for the evidence of recent ovulation in group 2. It will also be seen that there is no typical histological pattern of the ovaries which serves to distinguish either of these groups from the controls.

Hirsuties was considerable in three cases in group 1 while the other four showed slight excess of hair. In group 2 (patients who were ovulating) there was considerable hirsutism in four, and two showed a slight excess of hair. The other case in this group was interesting, because, though there was hirsuties of the face and trunk, the hair on her head was absent and she needed to wear a wig. Hirsuties was present in one case in the control group.

Lynch *et al.* (1959) noted a direct relationship between the degree of masculinization and the extent of luteinization of the theca cells. The present series of cases shows that there can be a marked degree of masculinization coincidental with ovulatory menstruation.

It will be seen from Table II that the operation of wedge resection has had no effect on the hirsuties of these patients, only one suggesting that she felt she was growing less hair after the operation, though there was no objective proof of this.

Obesity is no longer considered to be of importance in this syndrome (Stein, 1958), and it has not been a feature in our series of cases.

Hormone estimations were carried out on eight of the patients in groups 1 and 2. No abnormalities were found in the levels of the urinary 17-ketosteroids or the pituitary gonadotrophins.

Endometrial biopsies were taken in 11 cases. Of these, one showed no endometrium, and two showed a proliferative and one a secretory endometrium in the presence of a corpus luteum. The other seven showed cystic glandular hyperplasia. This is in contrast to Stein (1955), who found predominantly early proliferative endometrium, as did Ingersoll (1957) and Leclerq (1958). Jackson and Dockerty (1957) found mainly proliferative endometrium in a non-neoplastic group of

TABLE I.—*Histological Findings*

Case No.	Follicles			Lining of Follicles			Corpus Luteum	Endometrial Biopsy
	Cystic	Position	Atretic	Granulosa	Theca in Cystic Follicle	Theca in Stroma		
				Group 1				
1	Many	D/B	Many	Present	+ in cystic + ,, atretic	No	No	C.G.H.
2	Few	D	,,	Scanty	No	,,	,,	Nil
3	Many	D	Few	Present	± in cystic	,,	,,	C.G.H.
4	,,	D	,,	,,	+ ,, ,,	,,	,,	C.G.H.
5	Few	D	Many	,,	+ ,, ,,	,,	,,	C.G.H.
6	,,	B	,,	,,	+ ,, 3 atretic	,,	,,	Prolif.
7	Many	D/B	Few	,,	± ,, cystic	,,	,,	,,
				Group 2				
8	,,	B	,,	,,	+ in cystic	,,	Yes	—
9	,,	D	Many	,,	+ ,, ,,	,,	,,	C.G.H.
10	Few	D	Few	,,	± ,, ,,	,,	,,	C.G.H.
11	Many	D	,,	Scanty	± ,, ,,	,,	,,	Secretory
12	,,	D	,,	Present	+ ,, ,,	,,	,,	C.G.H.
13	Few	D	,,	,,	+ ,, ,,	,,	,,	—
14	Many	D	Many	,,	+ ,, ,,	,,	,,	—
				Group 3				
15	,,	B	Few	,,	± in cystic	,,	,,	—
16	,,	B	,,	,,	± ,, ,,	,,	No	—
17	,,	D	,,	,,	± ,, ,,	,,	Yes	—
18	,,	D	Many	,,	+ ,, ,, + ,, atretic	?	No	—
19	Few	D	Few	,,	± ,, cystic	No	Yes	—
20	Many	D/B	,,	,,	± ,, ,,	,,	No	—
21	,,	D	Many	,,	± ,, ,,	,,	,,	—

+ Signifies " within normal limits." ± Signifies " present." B = Bulging surface. D = Deep. C.G.H. = Cystic glandular hyperplasia.

TABLE II.—*Clinical Findings*

Case No.	Age	Menstrual Hist.	Fertility	Hirsuties	Obesity	Other Inf.	Follow-up
				Group 1			
1	21	Am. 9 mths.	0	Slight	Yes		Pregnancy
2	26	Men. 13, 7/28 to 17, then 2–14/6 to 12 mths.	0	Considerable	No		None
3	24	Men. 13, 6 to 12 mths.; Am. 14 mths.	0	Slight	,,		Pregnancy
4	26	Men. 13, 5/2 to 5 mths.	0	,,	,,		Reg. periods—relapse after 5 mths.
5	21	Men. 15, regular 1 yr., then Am. up to 1 yr.	0	,,	,,		Reg. periods till relapse after 6 mths.
6	25	Men. 13, Am. up to 1 yr. Wedge resection 2 yrs. ago = Am. up to 9 mths.	0	Considerable	Yes		No period, ? hirsuties less
7	19	Men. 12, 5/28 to age 15, then always irregular	0	,,	No		Reg. periods 3 mths.
				Group 2			
8	27	Men. 13, 5/28	1 child	Considerable	No		Periods 5/26
9	26	Men. 13, 7/28 for 8 yrs., then Am. up to 12 mths.	0	,,	Yes		,, regular
10	36	Men. 16, 6/2 to 3 mths.; Am. 8 mths.	0	Slight	No		None
11	25	Men. 11, 5/35, then Am. 16 mths.	0	Considerable	,,		Periods regular
12	32	Men. 12, 5/28 to age 27; then Am. 3 to 4 mths.	0	Face, trunk	,,		,, ,,
13	19	Men. 15, Am. up to 6 mths.	0	Slight	,,		,, ,,
14	34	Men. 16, Am. up to 6 mths.	1 child	Considerable	,,	Depression	Periods 5/21 for 6 mths., then amenorrhoea
				Group 3			
15	26	Men. 13, 5/1 to 6 mths.	0	No	No	Infertility. Hydrosalpinges	None
16	31	Men. 11, 6/28	1 child	,,	Yes	Dyspareunia	Normal
17	24	Men. 11, 7/1 to 2 mths.	0	,,	No	Ruptured luteal cyst	,,
18	17	Men. 12, 2/1 to 2 mths.	0	Considerable	,,	Enlarged ovary	Monthly periods
19	20	Periods 6/28	0	No	,,	Opn. for abdo. pain	Normal
20	34	Periods 4/1 to 3 mths.	1 child	,,	,,	Oophorectomy at opn. for backache	,,
21	26	Men. 15, 5/35	2 children	,,	,,	Enlarged ovary	,,

Men. = menarche. Am. = amenorrhoea.

cases, but noted the occurrence of endometrial carcinoma in cases with long histories. Kaufman *et al.* (1959) found a higher incidence of endometrial hyperplasia, as we have done. It may be suggested that the diagnosis in some of these cases should therefore be metropathia haemorrhagica. However, typical cases of metropathia haemorrhagica do not have periods of amenorrhoea lasting longer than three months. At this hospital cystic glandular hyperplasia is found more often than was formerly suspected, and it may occur in patients who are menstruating regularly. It is sometimes found in association with corpora lutea, and pregnancy has been seen to occur in a uterus which showed cystic glandular hyperplasia.

The earlier and larger series of cases quoted do not appear to have had routine endometrial biopsies taken, and it is possible that many more would have shown this histological picture.

The results of wedge resection in group 1 show that regular menstruation has not persisted for longer than six months, with the exception of two women who became pregnant two and three years respectively after operation. In group 2, where ovulation was occurring, of the six patients followed up, two had menstruated normally for more than a year. Regular menstrual periods had occurred in one patient for six months, but after this time she relapsed into amenorrhoea. The other three patients were still menstruating regularly at the end of four months, but a longer follow-up is not available. Stein (1958) has reported re-establishment of normal menstruation in 95% of patients, and 88% of his cases became pregnant.

Discussion

The aetiology of the Stein–Leventhal syndrome has received a great deal of attention and several theories have been advanced to explain it. However, the occurrence of the ovarian histological picture without symptoms, the absence of hyperthecosis, and the presence of corpora lutea in such a large proportion of the cases studied here make it difficult to accept any theory so far advanced. It has already been shown that it is not possible to pick out a case of this syndrome from the series presented. Since the appearance of the ovarian cells gives no true indication of the conditions which have produced this appearance we cannot go beyond reporting the features encountered in the cases seen at this hospital. The answer to the problem of aetiology is not likely to be found by ordinary histological examination.

It may be said that all our cases are in the early stages of a progressive disorder, but the age incidence is the same as that in published series. Symptomatology and histology do not necessarily go together, and it is difficult to believe that there is such a definite entity as a Stein–Leventhal syndrome.

The histological findings in the ovaries are shown to be present in the absence of symptoms, and it is strange that the only definite and constant part of the syndrome should occur also in the controls. It would be more apt to refer to the condition as multiple small follicular cysts of the ovary, rather than cling to the eponymous nomenclature suggesting symptoms and signs which may not be present.

If a patient is infertile and has palpably enlarged ovaries and no evidence of ovulation, there is adequate justification for the performance of wedge resection, which gives her a chance of ovulating and becoming pregnant.

Summary

Histological studies were made of the follicle linings in ovarian tissue from 21 patients.

The cases were divided into three groups, and the third of these groups was used as a control.

The histological and clinical features of the cases are discussed, and the conclusion is reached that the Stein–Leventhal syndrome does not appear to be a well-defined entity.

We are grateful to all the surgeons at Chelsea Hospital for Women for permission to use the case notes of their patients.

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THALASSAEMIA IN A GURKHA FAMILY

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The thalassaemia syndrome is occasionally encountered by clinicians in Gurkha (Nepalese) subjects, but there are few reports of cases in the literature. Brain and Vella (1958) reported haemoglobin-H disease (haemoglobin-H thalassaemia) in a Gurkha woman, and a second such case has recently been found, again in a pregnant Gurkha woman, in Malaya.

The present report deals with a case of thalassaemia-like disease in a young Gurkha girl. This diagnosis is supported by a family study.

Case Report

A female Gurkha child aged 3 months was seen at the British Military Hospital, Kinrara, in July, 1954, when she was referred for investigation for a hypochromic anaemia. Examination then revealed a relatively well-nourished infant with pallor of the mucous membranes and marked hepatosplenomegaly.

Laboratory investigations showed: haemoglobin, 5.5 g./100 ml.; W.B.C., 9,300/c.mm. (neutrophils 50% lymphocytes 40%, eosinophils 5%, basophils 3%, monocytes 2%); reticulocytes, 2%. Erythrocyte osmotic fragility was decreased. Peripheral blood films showed hypochromia, anisopoikilocytosis, microcytosis, target cells, and many normoblasts. No malarial parasites were noted on repeated

investigation. Bone-marrow films showed intensive normoblastic hyperplasia, but no malarial parasites or Leishman–Donovan bodies. Total serum bilirubin, 0.4 mg./100 ml.; indirect Coombs test negative; liver-function tests normal; Wassermann and Kahn reactions negative. Urine contained only traces of urobilinogen. Examination of faeces showed no evidence of ankylostomiasis. Radiological examination of the bones revealed no abnormality. A liver biopsy performed a few weeks later showed increased amounts of iron but normal histology.

Treatment consisted of large doses of iron, ascorbic acid, aneurine, pyridoxine, folic acid, vitamin B_{12}, thyroid, and cobalt. This had no effect in alleviating the anaemia. In January, 1956, a splenectomy was performed in the hope of lengthening the interval between blood transfusions. The histology of the excised spleen was normal, but increased amounts of iron pigment were noted. There was no noticeable improvement in her condition, and a subsequent course of cortisone therapy was also ineffective. So far she has been maintained on repeated transfusions of 500 ml. of packed cells each six-week period. In April, 1957, electrophoresis of her haemoglobin, performed on filter paper (*p*H 8.6 and 6.5) on a blood sample obtained prior to transfusion revealed only normal adult haemoglobin. The one-minute alkali denaturation test (Singer, Chernoff, and Singer, 1951) revealed 10% foetal haemoglobin. A diagnosis of thalassaemia was made, but it was not possible to carry out a family study until August, 1959.

A physical examination of the patient carried out in April, 1959, revealed a pale child of normal stature with normal mental development. The only abnormality was a firm enlargement of the liver, the edge of which was palpable 2 in. (5 cm.) below the level of the umbilicus. *X*-ray films of the skull and long bones showed no abnormalities. The results of haematological investigation at this time are shown in the Table.

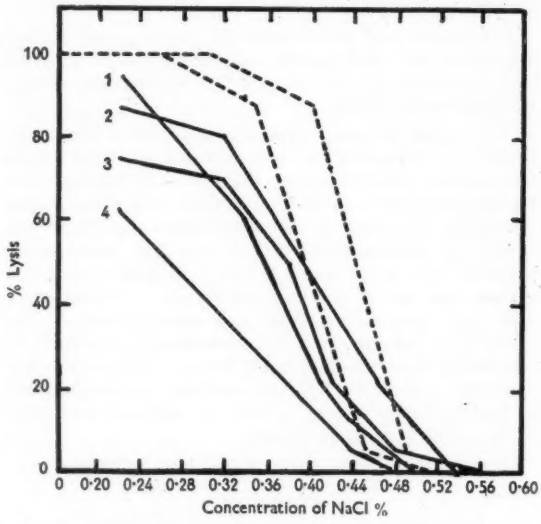
The patient is the fifth in a family of six children. The father is healthy and symptom-free, but the mother has a hypochromic anaemia which was detected during her last pregnancy and which has proved resistant to iron and ascorbic-acid therapy. The youngest in the family is a healthy infant, and the other four children are symptom-free. They are all normal in stature and appearance but rather pale, and none of them show enlargement of spleen or liver.

Results of haematological investigation in the family (excluding the youngest infant, 1 week old at the time of these investigations) are shown in the Table. Peripheral blood smears from each of the parents and the four siblings studied all showed hypochromia, marked anisopoikilocytosis, microcytosis, and occasional target cells. The haemoglobin-A_2 results given in the table represent the averages of duplicate estimations, using a starch-block electrophoresis technique essentially similar to that of Kunkell *et al.* (1957). The range for 79 healthy subjects by this method was 0.00–2.51%, average 1.78% (Vella, 1960). No abnormal haemoglobin components were detected, and no intra-erythrocytic inclusion bodies were elicited on supra-vital staining of erythrocytes with brilliant cresyl blue (Gouttas *et al.*, 1955), in any members of the family.

Results of Haematological Study of the Patient and Her Family

	Patient	Father	Mother	Brother	Sister	Brother	Sister
Age (in years)	5	30	28	6½	4	3	1½
Hb (g./100 ml.)	3·7	11·4	9·2	9·2	7·4	8·0	6·9
Red cells (millions/c.mm.)	1·61	4·0	3·78	3·1	3·2	2·8	2·5
Haematocrit (%)	17	41	32	34	29	30	Not done
M.C.V. (μ^3)	105	102	84	109	90	107	"
M.C.H. ($\mu\mu$g.)	22	26	24	29	23	28	27 "
M.C.H.C. (%)	24	28	28	27	25	26	Not done
Reticulocytes (%)	3·0	<0·5	<0·5	<0·5	<0·5	<0·5	<0·5
Target cells	++	−	−	−	−	−	−
Hypochromia	+	±	+	+	+	+	+
Anisopoikilocytosis	++	+	++	++	++	++	++
Microcytosis	+	+	+	+	+	+	+
Normoblasts	++	−	−	−	−	−	−
Haemolysis:							
Commences at % NaCl	0·48	0·52	0·49	0·56	0·56	0·56	0·52
Complete at % NaCl	<0·28	0·36	<0·24	<0·30	<0·24	<0·24	<0·24
Alkali-resistant Hb (%)	8·0	2·0	2·6	2·0	1·5	3·7	1·0
Hb A_2 (% of total)	1·00	5·56	4·0	4·28	3·45	5·50	3·21
Hb on electrophoresis	A	A	A	A	A	A	A

+ Indicates present; ++ indicates marked; ± indicates slight; − indicates absent.



Osmotic fragility curves from the patient and her family. 1=Mother. 2 and 3=Patient's siblings. 4=Patient.

Discussion

The early age at onset, the severe anaemia resistant to standard therapy, the peripheral blood picture, the marked hepato-splenomegaly, the evidence of visceral siderosis, and the subsequent course of the disease in this patient indicate thalassaemia or a thalassaemia-like disorder. The continued absence of radiological changes in the skull and long bones, and the normal physical development so far, may be due to regular blood transfusions from an early age. This may be responsible in some degree for her present liver enlargement. Relatively low levels of foetal haemoglobin are not unknown in thalassaemia major (Itano, 1955).

The finding of an iron-resistant hypochromic microcytic anaemia in the mother in the presence of 4.0% of haemoglobin A_2 suggests that she is heterozygous for the thalassaemia abnormality. Similarly, the mild anaemia and the presence of 5.56% haemoglobin A_2 in the father, even in the presence of a normal erythrocyte osmotic fragility curve, suggest that he also is a thalassaemia carrier. The anaemia in the siblings may well have a nutritional element, though the findings in both parents and the increased haemoglobin A_2 concentrations (3.21–5.56%) point to a thalassaemic background for their anaemia.

We are grateful to Major S. E. M. Jarvis, R.A.M.C., for his interest in this patient and in this report, and to Lieut-Colonel J. P. Baird, R.A.M.C., for his advice.

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Medical Memoranda

Herpes Zoster Occurring in a Patient with Chicken-pox

Clinical and epidemiological observations suggest that chicken-pox and zoster are caused by the one virus, and recent laboratory studies on the growth in tissue culture of virus from the two clinical entities support this view (Weller *et al.*, 1958 ; Weller and Witton, 1958). Though 2–5% of zoster patients develop a generalized rash, sometimes profuse enough to be typical of chicken-pox, it is much less common for chicken-pox patients to develop a secondary eruption with a typical zoster distribution. Stokes (1959) indicates that this is not an uncommon observation, but very few instances are recorded in the literature. Allen (1944) reported a case of chicken-pox in a boy aged 5 years who developed a zoster eruption on the right side of his body three weeks after the onset of chicken-pox. Cheatham *et al.* (1956) described the case of a 4-year-old boy suffering from a neuroblastoma with multiple metastases who developed chicken-pox and died 17 days after its onset. At necropsy a zoster eruption was found on the right side of the abdomen and back, corresponding to sensory innervation from T 10. Another example of a zoster eruption developing in a patient suffering from chicken-pox is mentioned below.

CASE REPORT

An outbreak of chicken-pox occurred in a boys' boarding-school. The onset of illness in the first case was on January 21. This was followed by eight other cases between February 5 and 7, and a further eight between February 21 and 25.

On March 12 the last case occurred in a boy of 8 years who had not had chicken-pox previously. His eruption was sparse, as in all the other cases in this outbreak. On March 18, when fresh lesions had not been noted for several days, 10 vesicles appeared in the right cervical sensory area (C 3). They were associated with extreme hyperaesthesia of the surrounding skin, as indicated in the accompanying Figure, and the patient, though otherwise feeling quite well, was very reluctant to undergo examination. The lesions became purulent by March 21, and had healed completely on April 11, by which date the skin sensitivity had disappeared. As the school was in quarantine, the patient could not have been in contact with a case of zoster since the beginning of term.

Vesicles in right cervical sensory area, associated with extreme hyperaesthesia of surrounding skin.

COMMENT

In zoster patients there is usually a history of previous chicken-pox. In those over 40 years, in whom the malady is most often seen, the history of an earlier chicken-pox infection may not be remembered ; but in children or adolescents suffering from zoster a history of previous chicken-pox is usually obtained (Schools Epidemics Committee, 1938). An earlier and greater rise of antibody had been found in the sera of zoster than in chicken-pox patients (Taylor-Robinson and Downie, 1959 ; Taylor-Robinson and Rondle, 1959) ; this is consistent with the view that zoster represents a second clinical infection with the virus. Little is known, however, about the pathogenesis of zoster. In the majority of zoster cases there is no known contact with chicken-pox or other zoster patients, and the seasonal prevalence of chicken-pox is not accompanied by an increased incidence of zoster (Seiler, 1949). These observations suggest that zoster is caused by the activation of latent chicken-pox virus. This view might help to explain the occurrence of zoster associated with disease or injury of the spine, *x*-ray therapy, or lumbar puncture. There is no evidence to indicate the tissue in which chicken-pox virus might lie latent nor, in most cases, the stimulus which leads to reactivation.

The occasional occurrence of cases such as that reported above indicates that chicken-pox virus may infect root ganglia at the time of the original chicken-pox infection, and suggests the possibility that in zoster cases the virus might remain latent in nerve tissue between the primary attack of chicken-pox and subsequent zoster. The occurrence of pain and hyperaesthesia involving the area of skin or mucous membranes, where the rash is to appear several days later, indicates that spread of virus occurs peripherally from the ganglia to the skin, probably by nerve pathways. This sequence of events is supported by histological evidence.

I thank Professor A. W. Downie for his advice and help in preparing this paper, and Dr. E. L. Roberts, of Formby, for allowing me to see his patients.

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Reviews

£.S.D. OF SOCIAL SECURITY

The Cost of Medical Care. (Pp. 216+xiii. 9s.) Geneva: International Labour Office. 1959.

Only those who have tried to obtain information about the cost of medical care in different countries and to compare them realize what a complex, if not impossible, task it is to be sure that like is being compared with like. This valuable study recognizes its limitations, but it is the best yet published. It provides information about the range of benefits provided by social security schemes, and, in order to overcome differences in the cost of living and in official currency exchange rates, it sets out expenditures as percentages (1) of the average national income per head of the population, (2) of the average income per economically employed active person, and (3) of the reference wage—the average annual wage of an unskilled worker in the manufacture of machinery other than electrical—for each country. This method of comparing one country with another is the only practicable one. The figures were collected in 1955 and no doubt changes have occurred since then.

It is only in England and Wales and in New Zealand that the whole population is covered, but the study deals with the following countries where there is some form of social security: Belgium, the Swift Current District of the Province of Saskatchewan in Canada, Chile, Denmark, England and Wales, France, Federal Republic of Germany, Italy, Mexico, the Netherlands, New Zealand, Norway, Switzerland, and Venezuela. Figures are also given of private expenditure on medical care in the United States. For all countries the figures are provided, where available, year by year from 1945. One would have liked to see them for countries such as Sweden, Finland, and Russia but presumably they were unobtainable.

The chapter headings are: persons protected and the contingencies covered; expenditure on medical benefits and the actual cost of providing the care; subsections on medical practitioner care, drugs, hospital care, dental care and "residual care" which brings in the supply of spectacles, health visiting and home nursing, after-care, the cost of medical auxiliaries, and the supply of ambulances; trends in expenditure on medical care; and incomes of medical practitioners. There are 53 pages of appendices and tables.

It is a unique work of reference for the administrator and politician, and a quarry into which those with statistical or polemical minds can dig to their hearts' content and produce some fact to confound their opponent. When the figures for England and Wales are out of line with other countries it is an exercise in ingenuity to try to think why it should be so, but the reasons are generally baffling even to those with a wide and detailed knowledge of the English system.

Among interesting pieces of information are the following: England is among the low-cost countries for pharmaceutical supplies; it is average for the cost of general practitioner services; it is among the highest for hospital care and within that field this is mainly due to the cost of maintaining the hospital and nursing the patients rather than to payments to doctors; England is the only country where the expenditure per person protected, expressed as a proportion of the national income, is declining.

The main conclusions are that where expenditure on social security is rising it is chiefly due to hospital costs, and that rising costs can be checked by improved domiciliary care, shortening the patient's length of stay in hospital, and keeping a close check on the use of auxiliary services. "The present study . . . indicates that they [medical costs] have not risen any faster than national income or reference wages, although hospital costs show a certain tendency to outstrip the rest."

ALLEN DALEY.

TREATMENT OF BONE AND JOINT T.B.

Surgical Treatment of Bone and Joint Tuberculosis. By Robert Roaf, M.A., M.Ch.Orth., F.R.C.S.Ed., F.R.C.S.Eng., W. H. Kirkaldy-Willis, M.A., M.D., B.Chir., F.R.C.S.Ed., and A. J. M. Cathro, M.B., Ch.B. Foreword by Harold Boyd, M.D., F.A.C.S. Illustrated by W. Connell, M.C.S.P. (Pp. 137+viii. 30s.) Edinburgh and London: E. and S. Livingstone, Ltd. 1959.

This book is a practical guide, and in it are described the principles of operative surgery for tuberculosis of the bones and joints advised in conjunction with antibiotic therapy. The opinions expressed refer particularly to Africans and Asians, whose social and economic problems, including the exiguousness of the hospital service, make it difficult for the doctor to provide ideal therapy for raising the patient's resistance. It is thought that racial immunity to antibiotic drugs may develop and complicate the progress now being made. It is stated dogmatically that chemotherapy has changed the demand for surgery and brought to the surgeon's notice the possibility of getting his patient a good joint quickly. Further, the type of operation recommended, when required, is not the one that was considered advisable in the pre-antibiotic era. Although the authors treat each case on its own merits, there is a tendency to greater systematization as the prognosis is now easier to assess and may depend on manifestations of tuberculosis elsewhere than in the skeleton.

A small portion of the text is given to general considerations, and the bulk is concerned with regional bony tuberculosis. Some aspects of diagnosis and pathology are described, but no attempt is made to provide detailed differential diagnoses. The signs of joint disease and the frequency of abscess formation in Africans are comparable to those seen in patients who came to hospitals in North America and Great Britain fifty years ago. Little reference is made to signs which are of importance in spotting early and slight infection of joints, but biopsy is recommended when the diagnosis is uncertain. The description of regional variations in disease is lucid, though there is no information about how treatment should be varied when resistance is below normal and there are serious lesions elsewhere in the body.

The pattern of routine treatment is well described. The dosage of streptomycin and other drugs is decided on clinical grounds, and arthrodesis is carried out in 90% of cases. The intra-articular has replaced the extra-articular operation and is usually done in two stages—first to remove abscess contents, debris, and sequestra; and, secondly, to provide a fusion, sometimes using a bone graft passing through the infected area. For spinal disease, which is frequently complicated by paraplegia in Africans, a one-stage débridement-fusion operation is preferred. The surgical approach to each area of the spine is described, and if the operation becomes hazardous a débridement only is carried out. In the case of the hip early arthrodesis is advised if there is affection

of articular cartilage. The immobilization of hip and knee is relatively short. The ankle is stated to respond well to treatment.

The battle against tuberculosis in many countries is almost won, but in far more it is still a menace, and this book will help those who are fighting the disease by chemotherapy and surgery.

ST. J. D. BUXTON.

PRACTICAL CARDIOLOGY

A Clinical Introduction to Heart Disease. By Crighton Bramwell, M.A., M.D., F.R.C.P. (Pp. 229; illustrated. 21s.) London: Oxford University Press. 1959.

This is an attractive practical little book, and the price is very moderate. Most of the information that a senior student or young practitioner needs is clearly set out, though it seems a little unusual to find the section on treatment coming before the description of the circulatory failure for which the treatment is required. There are numerous case histories, for the most part clear and interesting and to the point. Some might have been made a little shorter in some respects, but with what seem to be the omissions filled in.

There is nothing in the book about the effects on the circulation of the constricted pericardial sac, nor about tamponade; unipolar leads are now so universally familiar that their value in the diagnosis of an infarct might have been more fully discussed. Hardly enough detail is given about the signs and symptoms of auricular flutter—not so very uncommon—to enable one to suspect when it is present. However, the author always makes a close correlation between disease and physiology, which is satisfactory.

Throughout the book the author uses his great experience to illustrate points and stress what is important. There are plenty of good illustrations, pulse tracings, and cardiograms. This book can be well recommended as a clear and simple exposition of the subject of heart disease.

TERENCE EAST.

THE ACTIVITY OF ENZYMES

The Enzymes. Edited by Paul D. Boyer, Henry Lardy, and Karl Myrbäck. Second edition, completely revised. Volume I. *Kinetics, Thermodynamics, Mechanism, Basic Properties.* (Pp. 785+xi; illustrated. $24.) New York: Academic Press Inc. 1959.

This is the first tome of a new edition of the definitive work of the same title which appeared under the editorship of the late Professor J. B. Sumner and Professor Karl Myrbäck between 1950 and 1952. The main emphasis of the work is on the properties, mechanism of action, and chemistry of enzymes, and metabolic functions are not stressed. The present volume deals with enzyme kinetics, the fundamental chemistry of the enzyme-catalysed process and its mechanism, protein structure and enzyme activity, induced formation of enzymes, and the control of enzyme activity. Volume II will be concerned with the chemistry and role of enzyme co-factors, and subsequent volumes will be concerned with individual enzymes or enzyme systems. The treatment makes the work more one of reference than for general reading, but for those who need a succinct summary, written by an expert, of knowledge under each of the headings in this first volume, this book can be strongly recommended.

F. G. YOUNG.

HAEMATOLOGICAL PROGRESS

Progress in Hematology. Volume II. Edited by Leandro M. Tocantins, M.D. (Pp. 290+vi; illustrated. $9.75.) London and New York: Grune and Stratton. 1959.

This interesting book is the second of what is likely to be a series of progress reports on haematology. It contains a baker's dozen of articles on subjects ranging from the dynamic cytology of the blood, as revealed by phase-contrast cinematography, to the latest operative technique for oesophageal varices. The majority of the articles are reviews, and the interest in clinical research is to-day so great, particularly in the United States, that it is inevitable that some of them deal with subjects which have already been reviewed in a variety of other journals. A new idea is pretty soon thrashed out nowadays, and the amount written about erythropoietin or the transfusion of bone-marrow in the treatment of radiation injury has already outstripped the actual advance of knowledge. However, there is something here for all tastes, and haematologists in particular will find it helpful to have these readable summaries of the present position of their subject.

Bessis's article on phase-contrast cinematography will be of interest to many because it actually illustrates processes such as the enucleation of the erythroblast and the formation of platelets by megakaryocytes which would have remained hypothetical so long as cells had to be studied in the fixed state. Wilkinson and Turner's chapter on the chemotherapy of chronic myeloid leukaemia, with special reference to myleran, is valuable because it confirms the suspicion that this useful and convenient drug probably increases the proportion of patients in whom the terminal event is an acute myeloblastic change in the character of the disease. The book is beautifully produced and the articles are well documented with lists of references. Indeed, it is almost too elegant and expensive for a progress report.

L. J. WITTS.

ABNORMAL CONNECTIVE TISSUE

Chronische Krankheiten des Bindegewebes. Beiträge zur Pathologie und Klinik der Organ- und Systemsklerosen. By Professor Dr. Rolf Emmrich. (Pp. 280+ix; illustrated. DM. 41.60.) Leipzig: VEB Georg Thieme. 1959.

It is difficult to give a fair yet critical estimate of this kind of book. Certainly there is a place at the present moment for a general survey of the clinical disturbances arising from abnormal connective tissue, but where is one to draw the line? No one will deny that something useful has come from the concept of "collagen diseases," though the early enthusiasm with its talk of a new direction in medicine seems hardly to have been sustained. But is one justified in lumping coronary sclerosis, osteomyelosclerosis, cirrhosis of the liver, diabetic retinopathy, for instance, together with vascular collagen diseases—polyarteritis nodosa, lupus erythematosus, and the like—and rheumatism? Professor Emmrich may, of course, be blessed with prescience that is not shared by most of us. I confess that I found such grouping annoying and was not impressed by the meagre evidence offered in its support.

Nevertheless there is much in this modest volume that catalyses the imagination and helps the investigator over the obstacles of a desperate section of medicine. Special praise can be given to the section on diagnosis and treatment, while the pathologist will find something

to interest him in the discussion of hyaline and amyloid, and in the sensible account of the chemistry of connective tissue. References are well selected and generous, the illustrations and index adequate.

ROY CAMERON.

ASPECTS OF AGEING

The Process of Aging in the Nervous System. Edited by James E. Birren, Ph.D., Henry A. Imus, Ph.D., and William F. Windle, Ph.D., Sc.D. With 32 contributors. (Pp. 224+xii; illustrated. 52s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

The topic of old age is important enough to warrant yet another serious contribution. Modern improvements in histological techniques and the use of microchemical methods have opened new vistas as far as our knowledge of the senile changes within the nervous system is concerned. Thirty-two scientists assembled in order to discuss the basic processes of ageing, to summarize the present state of our knowledge, and to seek new "guide lines and approaches" for future research. This little book contains 11 set texts dealing with various aspects of the problems. Not unnaturally the standard achieved could not be maintained at a steady level, though some of the chapters certainly form important contributions. In addition, however, the editors have reproduced the text of various panel discussions which arose in the course of the symposium.

The growing practice of indulging in table-talks on a given theme is not altogether a wise one, and the present-day transatlantic habit of treating seriously these off-the-cuff interventions, and even printing them, is rarely a credit either to the author's good sense or to his command of language. It is the reviewer's hope that British medicine will avoid these informalities whenever serious subject-matter is under scrutiny.

MACDONALD CRITCHLEY.

PHYSICS IN MEDICINE

Physics and Electronics in Physical Medicine. By A. Nightingale, M.A., Ph.D., F.Inst.P. Foreword by F. S. Cooksey, O.B.E., M.D., F.R.C.P. (Pp. 292+x; illustrated. 30s.) London: G Bell and Sons, Ltd. 1959.

The author tells us that he wrote this book to give an account of the physical principles underlying physical medicine. He has succeeded admirably. The first half of the book is devoted to fundamentals of physics, and here the style is clear and neither too simple nor too complicated. This is a refreshing change from some of the textbooks through which the postgraduate is expected to wade. The second half deals with applications of physical agents in medicine. No exaggerated claims are made for the effects of these, and the whole subject is examined factually and objectively. The third section of the book is labelled "appendices." This strange term reveals a most valuable series of articles on electrodiagnosis, electrical stimulation, ultrasound, transistors, and other such important subjects. The bibliography is well arranged and extensive and the index is complete.

This book can be recommended for doctors, physiotherapists, and any others who want a straightforward up-to-date textbook on the application of physics to medicine.

W. S. TEGNER.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Struggle to Return. Being an Account of an Operation for a Tumour on the Brain—and of the Remarkable Recovery Therefrom. By Carol Bunker. (Pp. 232. 18s.) London: Peter Davies. 1960.

Recent Advances in Clinical Pathology. Series III. By various authors. General editor: S. C. Dyke, D.M.(Oxon.), F.R.C.P.(Lond.). (Pp. 425+xii; illustrated. 50s.) London: J. and A. Churchill, Ltd. 1960.

Cardiac Resuscitation. Edited by J. Willis Hurst, M.D. (Pp. 141+ix; illustrated. 44s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Principles and Methods of Clinical Chemistry for Medical Technologists. By Eugene W. Rice, Ph.D. (Pp. 286+xvii; illustrated. 56s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

General Psychotherapy. An Outline and Study Guide. By John G. Watkins, Ph.D. (Pp. 255+xxviii. 74s.) Springfield, Illinois: Charles C. Thomas Oxford: Blackwell Scientific Publications. 1960.

Modern Problems in Pediatrics. Edited by A. Hottinger and H. Berger. Volume V. *Child Development: An International Method of Study.* Edited by Frank Falkner. (Pp. 237+x; illustrated. Sw.fr. 50.) Basle, New York: S. Karger. 1960.

Health Service, Society, and Medicine. Present Day Health Services in Their Relation to Medical Science and Social Structures. By Karl Evang, M.D. University of London Heath Clark Lectures, 1958. (Pp. 171+viii. 21s.) London, New York, Toronto: Oxford University Press. 1960.

L'Ernia Vaginale del Douglas o Elitrocele. By Eugenio Lenzi. (Pp. 137; illustrated. L. 1,500.) Pisa: Edizioni "Omnia Medica." 1960.

Rose and Carless: Manual of Surgery. Consulting editor: Sir Cecil Wakeley, Bt., K.B.E., C.B., LL.D., M.Ch., D.Sc., F.R.C.S., F.R.S.E., F.A.C.S., F.R.A.C.S. Editors: Michael Harmer, M.A., M.B., B.Chir.(Cantab.), F.R.C.S., and Selwyn Taylor, M.A., D.M., M.Ch.(Oxon.), F.R.C.S. Assisted by 15 contributors. Nineteenth edition. (Pp. 1,389+xv; illustrated. 84s.) London: Baillière, Tindall and Cox. 1960.

Clinical Tropical Diseases. By A. R. D. Adams and B. G. Maegraith. Second edition. (Pp. 540+x; illustrated. 52s. 6d.) Oxford: Blackwell Scientific Publications. 1960.

Microchemical Methods for Blood Analysis. By Wendell T. Caraway, Ph.D. (Pp. 109+xi. 42s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Food Enrichment in South Africa. A Study of Principles of Food Enrichment and Their Application to Food Policy in South Africa, with Special Reference to the Use of Fish Flour for the Protein Enrichment of Bread. National Nutrition Research Institute. C.S.I.R. Research Report 172. (Pp. 157+xiii; illustrated. 21s.) Pretoria: South African Council for Scientific and Industrial Research. 1959.

Design of Documents. A Study of Mechanical Aids to Field Enquiries. By Lancelot Hogben, F.R.S., and K. W. Cross, Ph.D. (Pp. 88; illustrated. 35s.) London: Macdonald and Evans, Ltd. 1960.

Handbook of Haematological and Blood Transfusion Technique. By J. W. Delaney, F.I.M.L.T. (Pp. 311+x; illustrated. 45s.) London: Butterworth and Co. (Publishers) Ltd. 1960.

General Anaesthesia for Dental Surgery. By R. S. Walsh, M.A., B.M., B.Ch., F.F.A. R.C.S. (Pp. 94+ix; illustrated. 21s.) London: Longmans. 1960.

Cole and Elman Textbook of Surgery. By Warren H. Cole, M.D., with 49 contributing authors and consultants. Seventh edition. (Pp. 1,224+xxi; illustrated. £7 7s.) London: Staples Press. 1960.

Cardiac Auscultation including Audio-visual Principles. By J. Scott Butterworth, M.D., Maurice R. Chassin, M.D., Robert McGrath, M.D., and Edmund H. Reppert, M.D. Second edition (revised and enlarged). (Pp. 102; illustrated. $6.25.) New York and London: Grune and Stratton. 1960.

Tejido Conectivo y Enfermedades del Colageno. By Mario F. Villamil and Roberto E. Mancini. (Pp. 379+xviii; illustrated.) Buenos Aires: Lopez and Etchegoyen, S.R.L. 1959.

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ERYTHROCYTE SEDIMENTATION RATE

The sedimentation rate of the red cells is one of the most frequent clinical laboratory determinations requested to-day, and rightly so, because the performance is simple and the result of considerable clinical value. It was first introduced as a diagnostic test for pregnancy,[1] but it was soon found to be valueless as a specific diagnostic criterion of any one disease. Indeed, its great value lies in its complete lack of specificity, for it is raised in any condition associated with inflammation (except when purely localized) or breakdown of tissue. Like fever, leucocytosis, increase in blood viscosity, and the presence of C-reactive protein, an increase in the E.S.R. is a manifestation of the body's reaction to injury—one of the so-called acute-phase reactants. The great value of the E.S.R. therefore lies in indicating progress in those chronic diseases such as tuberculosis[2] or rheumatoid arthritis in which it waxes and wanes with the activity of the disease.

The rate at which the red cells sediment is the resultant of many conflicting factors affecting both the cells and the plasma. The most important are the concentrations of the various plasma proteins, especially fibrinogen and α_2 and γ globulin. The clearest correlation between the E.S.R. and plasma constituents has been obtained by J. Hardwicke and J. R. Squire.[3] Since the viscosity of the plasma must exert a retarding effect on sedimentation, and since the sedimenting force itself is the difference in specific gravity between the cells and the plasma, it is essential if results in different specimens are to be compared to correct for these two variables. Furthermore, since the ratio of cell volume to plasma volume also considerably affects the E.S.R., comparable results can be obtained only if this ratio is kept constant. Hardwicke and Squire, therefore, introduced the concept of a maximum corrected sedimentation velocity. This is the maximum observed velocity when the packed cells constitute 30% of the total volume; a correction is applied for any variation from normal in plasma viscosity and for difference between specific gravity of cells and plasma. By the addition of various macromolecules such as dextran, fibrinogen, gelatine, or gum acacia, they were able to show that the E.S.R. is almost entirely dependent on the concentration in the plasma of such asymmetric macromolecules as fibrinogen, and the α_2 and γ globulins. Owing to differences both in molecular weight and in molecular asymmetry, these various plasma proteins are by no means equally effective in accelerating erythrocyte sedimentation, the effects of the three proteins in equal concentration being approximately in the ratio 10:5:2.

A raised E.S.R. is therefore an indication of an increase in the plasma of one or more of those proteins which by virtue of their asymmetric shape encourage the aggregation of the red cells into clusters or rouleaux. The enormous variety of pathological states associated with a raised E.S.R. is thus no longer surprising, since almost all infections, both acute and chronic, are associated with a rise in both α_2 and γ globulins, and most wasting and destructive diseases tend to be associated with an increase in fibrinogen. The E.S.R. is merely a simple, rapid, and fairly crude method by which these changes in plasma proteins may be readily revealed. Similar but more precise information is obtainable by electrophoretic analysis or more simply by the determination of plasma and serum viscosity.

Owing to the much greater labour entailed, neither of these tests seems likely to oust the E.S.R. from its present popularity in clinical medicine. It is therefore of considerable importance that the technique of the test should be above suspicion. Of the two most widely used methods, that introduced by M. M. Wintrobe[4] was much favoured because the same sample of blood could serve not only for the estimation of the E.S.R. but also for determining the haematocrit, and hence showing if any correction was required as a result of anaemia. Unfortunately, several workers[5–7] have reported studies in which parallel determinations of the E.S.R. with both the Wintrobe and the Westergren methods have produced widely divergent results. In the great majority of these the E.S.R. was considerably raised by the Westergren method while the Wintrobe result was often within the normal range. Collateral evidence indicated that the correct result was the one given by the Westergren method. Several factors are now known to contribute to the unreliability of the Wintrobe method, but the principal is the type of

[1] Fähraeus, R., *Acta med. scand.*, 1921, **55**, 1.
[2] Clegg, H. A., *Tubercle*, 1929, **10**, 205.
[3] Hardwicke, J., and Squire, J. R., *Clin. Sci.*, 1952, **11**, 333.
[4] Wintrobe, M. M., *Amer. J. med. Sci.*, 1933, **185**, 58.
[5] Gilmour, D., and Sykes, A. J., *Brit. med. J.*, 1951, **2**, 1496.
[6] Goldberg, S., Glynn, L. E., and Bywaters, E. G. L., ibid., 1952, **1**, 202.
[7] Goldberg, A., and Conway, H., ibid., 1952, **2**, 315.
[8] Shannon, F. T., and Bywaters, E. G. L., ibid., 1957, **2**, 1405.

anticoagulant used. The technique according to Westergren results in the dilution of the blood sample by one part of 3.8% citrate solution to four parts of whole blood; no dilution occurs with the Wintrobe technique, since the anticoagulant is used in solid form. When the blood shows a high serum viscosity as well as a high haematocrit, anomalous results might well occur with the undiluted blood, since the high viscosity retards both the downward movement of the cells and the corresponding upward displacement of the plasma, while the high concentration of cells impedes sedimentation at all values of plasma viscosity. As F. T. Shannon and E. G. L. Bywaters[6] rightly point out, the higher the haematocrit the greater the quantity of plasma displaced per unit of sedimentation, and with plasma of high viscosity the frictional resistance between the plasma and the wall of the tube becomes the limiting factor. The essential correctness of this view is shown by the fact that of nine samples that gave discordantly low readings in the standard Wintrobe tube seven gave readings concordant with the standard Westergren results when the test was performed in wide tubes—namely, 4–5 mm. in diameter.

To avoid the difficulties and anomalous results occasionally met with, many modifications of technique have been introduced. One of the latest is discussed this week by Dr. J. B. Dawson at p. 1697 of this journal. It is interesting to note that the method he recommends is to use solid sequestrene as the anticoagulant but to dilute the sample by a further addition of one part 3.8% citrate to four parts of blood. In accordance with the principles outlined above, this has been found to give reliable results.

TREATMENT OF TROPHOBLASTIC TUMOURS

Recent developments have emphasized the unique position of trophoblastic tumours in the study of human cancer and its treatment. These tumours vary in their behaviour from the benign hydatidiform mole through various degrees of malignancy to the chorionic carcinoma, with its remarkable capacity for vascular embolization. Though the usual course of choriocarcinoma leads rapidly to death, cases have occasionally been reported in which distant metastases have regressed either spontaneously or after surgical removal of the primary tumour.[1]

There has been speculation on whether this regression and similar behaviour by other tumours are due to the production of anti-tumour antibodies. In the case of trophoblastic tumours an immune response by the host might be expected, since the tumour is thought to be foetal in origin and if so obtains part of its genetic structure from the male. The concept of these tumours as homografts led I. Doniach and colleagues[2] to immunize a patient who had choriocarcinoma with leucocytes and skin from her husband with the object of inducing rejection of the tumour homograft. Evidence of an augmented immune response to the husband's tissue was obtained, and it was thought that temporary benefit to the patient had resulted.

Another approach to treatment has come from the observations that both the foetus and the maternal genital tract have a high requirement for folic acid, and R. Hertz therefore postulated that folic-acid antagonists might be of value in the treatment of this and allied tumours. Hertz and colleagues[3] have now reported on 27 women with metastasized trophoblastic tumours, of which 19 were choriocarcinoma. After treatment with an anti-folic-acid drug five had complete remission, 16 had remissions with evidence of residual disease, and six had an initial response but subsequently died. Five cases showed no response, but four of these had only one course of treatment. When complete remission was obtained, the patients have remained well without further therapy.

The folic-acid antagonist used by Hertz was methotrexate (4-amino-N-10-methyl pteroylglutamic acid) given in doses of 10–30 mg. daily by mouth in courses of five days. Death was partly attributable to therapy in three of the cases reported by Hertz, and all patients experienced severe side-effects. The chief of these were depression of bone-marrow, especially of the neutrophils, and stomatitis, proctitis, diarrhoea, jaundice, skin changes, and alopecia. After regression of the side-effects in each course, further treatment (up to 22 courses) was given, and this intermittent treatment lasted for six months or more. Permanent damage as a result of the drugs has not been observed in surviving cases. Other authors have also reported both successes and failures with this treatment,[4,5] and the study of combinations of cytotoxic agents in the treatment of choriocarcinoma is being undertaken both in Great Britain and the U.S.A. K. D. Bagshawe and W. D. W. Brooks[4] have reported the successful use of methotrexate and 6-mercaptopurine administered simultaneously. Other

[1] Park, W. W., and Lees, J. C., *A.M.A. Arch. Path.*, 1950, **49**, 205.
[2] Doniach, I., Crookston, J. H., and Cope, T. I., *J. Obstet. Gynaec. Brit. Emp.*, 1958, **65**, 553.
[3] Hertz, R., Bergenstal, D. M., Lipsett, M. B., Price, E. B., and Hilbish, T. F., *J. Amer. med. Ass.*, 1958, **168**, 845.
[4] Bagshawe, K. D., and Brooks, W. D. W., *Lancet*, 1959, **1**, 653.
[5] Buckle, A. E. R., *Brit. med. J.*, 1959, **2**, 1210.
[6] Li, M. C., *Proc. Amer. Ass. Cancer Res.*, 1959, **3**, 37.
[7] —— Hertz, R., and Bergenstal, D. M., *New Engl. J. Med.*, 1958, **259**, 66.
[8] Delfs, E., *Ann. N.Y. Acad. Sci.*, 1959, **80**, 125.

drugs have also been tried.[6] Testicular chorio-carcinomata do not appear to be highly sensitive to anti-folic-acid drugs.[7]

It is possible that choriocarcinoma will prove to be the first of the malignant tumours to have been eradicated by chemotherapeutic agents, and if so it will not be mere coincidence that it has occurred in the case of tumours whose growth activity can be reliably assessed.[8] The availability of accurate and sensitive methods for the estimation of gonadotrophins in the blood and urine is an invaluable guide to their treatment. The need for continued therapy is indicated by raised gonadotrophin levels long after clinical and radiological remission has occurred. It is no longer adequate to rely on the commonly used pregnancy tests as a guide to the treatment of these tumours, as these tests are generally too insensitive.

The severe toxic effects resulting from nearly lethal doses of cytotoxic agents are difficult to control. Antibiotics and blood transfusions are commonly given, while folinic acid and storage of bone-marrow, with subsequent replacement, may provide some defence against severe depression of the marrow. The rarity of these tumours and the need for complex measures to control treatment make it advantageous for both the patients and for medical knowledge that therapy should be undertaken only in the few centres with special facilities for it. There is still much to learn about the best treatment of these tumours. Meanwhile a registry has been set up (see p. 1749) to help to gather data on trophoblastic tumours of all types.

HYPOGLYCAEMIA IN THE NEWBORN

The blood-sugar levels of full-time newborn infants are often abnormally low by adult standards, yet these low values are not associated with clinical signs of hypoglycaemia.[1 2] In premature infants even lower levels are to be found without related clinical disturbances.[3 4] The mechanism whereby the low values are maintained is not understood nor are the reasons for the absence of symptoms.

In the first few days of life there is a slow but prolonged response to the glycogenolytic action of adrenaline, whereas the response to intravenous glucose is normal.[5] On the other hand glucagon produces an abnormally prolonged hyperglycaemia in full-time and premature infants during the first five days of life.[6] These findings may indicate immaturity of enzyme action, and it has been shown in animals that glucose-6-phosphatase activity in the liver is much diminished before birth.[7] The spontaneous rise in blood-sugar levels with age is consistent with the maturation of an enzyme system. Another group of infants in whom very low levels of blood sugar are to be found, especially in the first few hours of life, are those born to diabetic mothers.[3 8-10] It has been suggested that symptoms such as cyanosis, listlessness, hypotonicity, and twitchings, which are frequent in these infants, might be due to hypoglycaemia.[8] Consequently some paediatricians have given glucose feeds during the first eight hours of life.[9 11] However, most now hold the view that there is no relationship between the hypoglycaemia and abnormal signs of this type.[9 10] The signs are due to various other causes such as anoxia, intracranial haemorrhage, infection, and congenital heart disease. Glucose supplements during the first few hours of life have been abandoned in most units for premature babies. The present tendency among paediatricians, who are well aware of the frequency with which hypoglycaemia occurs in the newborn, has been to doubt whether it accounts for any of the respiratory or convulsive "incidents" which are so common at this age.

However, M. Cornblath and colleagues[12] have recently described such incidents in eight infants who were born to mothers suffering from pre-eclamptic toxaemia, and attributed them to hypoglycaemia. Six infants weighed less than 2.5 kg. (5½ lb.) at birth, and two weighed more. In six cases the labours were complicated by other abnormalities, in two delivery was normal (both of infants under 2.5 kg.). All the infants did fairly well until the onset of symptoms between 40 and 57 hours of age. The first signs were listlessness and refusal to suck. Subsequently they developed apnoea, hypotonicity, cyanosis, twitchings, and convulsions. Blood-sugar levels at this stage ranged from 1 to 24 mg. per 100 ml. The diagnosis was suggested in some cases by a low level of sugar in the cerebrospinal fluid. When the blood-sugar levels were raised by the administration of 10 or 50% glucose by intravenous injection or infusion the symptoms were immediately alleviated. This treatment had to be continued for several days before spontaneous recovery ensued. In

[1] Norval, M. A., Kennedy, R. L. J., and Berkson, J., *J. Pediat.*, 1949, **34**, 342.
[2] Farquhar, J. W., *Arch. Dis. Childh.*, 1954, **29**, 519.
[3] Miller, H. C., and Ross, R. A., *J. Pediat.*, 1940, **16**, 473.
[4] Norval, M. A., ibid., 1950, **36**, 177.
[5] Desmond, M. M., ibid., 1953, **43**, 253.
[6] Cornblath, M., Levin, E. Y., and Marquetti, E., *Pediatrics*, 1958, **21**, 885.
[7] Nemeth, A. M., *J. biol. Chem.*, 1954, **208**, 773.
[8] Hartmann, A. F., and Jaudon, J. C., *J. Pediat.*, 1937, **11**, 1.
[9] Komrower, G. M., *Arch. Dis. Childh.*, 1954, **29**, 28.
[10] Farquhar, J. W., ibid., 1956, **31**, 203.
[11] Reis, R. A., De Costa, E. J., and Allweiss, M. D., *Amer. J. Obstet. Gynec.*, 1950, **60**, 1023.
[12] Cornblath, M., Odell, G. B., and Levin, E. Y., *J. Pediat.*, 1959, **55**, 545.
[13] McQuarrie, I., *Amer. J. Dis. Child.*, 1954, **87**, 399.
[14] Sherman, H., ibid., 1947, **74**, 58.

one case the additional parenteral administration of A.C.T.H. and cortisone produced rapid restoration of skin colour and muscle tone. The responses to intravenous glucagon, intramuscular adrenaline, and oral casein or leucine in three infants were variable and difficult to interpret. It is clear that these cases, which had a self-limited course of several days' duration, were quite different from the rare examples of spontaneous symptomatic hypoglycaemia which appears in the neonatal period but lasts much longer.[13 14] In both types, however, there was apparently a rapid response of the clinical disturbances to the administration of glucose.

It is notoriously difficult to interpret cause and effect in the ill newborn infant. His capacity for abnormal behaviour is, like his capacity for normal behaviour, strictly limited. Various causes, such as anoxia, intracranial haemorrhage, and infection, can produce very similar clinical signs. This is particularly true of the premature infant. It is to be noted that 5 of the 8 infants described by Cornblath and his colleagues continued to show very low levels of blood sugar even after their symptoms had disappeared and administration of glucose had been stopped. Two infants remained spastic and mentally retarded, and though this could have been attributable to hypoglycaemia the initial incidents in the neonatal period could equally have been due to brain damage. One infant died of *Pseudomonas* sepsis. The initial response of all eight infants to parenteral glucose makes it very probable that hypoglycaemia was, at least in part, responsible for the symptoms and signs. It is important, however, that similar observations should be made on a larger series of cases. It would be unwise to administer intravenous glucose solutions to premature infants unless the presence of hypoglycaemia is proved and until other causes for the symptoms have been excluded, because hypertonic solutions might dangerously increase the volume of the blood.

ECZEMA AND SOAP

Eczema of the hands in the housewife is one of the general practitioner's commonest and most intractable problems. In his uncertainty about its true cause he may tentatively accept the patient's assertion that soap and household detergents must be held responsible. The dermatologist, with a show of confidence which he will usually admit is grounded on clinical impressions and prejudices rather than on solid experimental evidence, may either support those opinions or partially or completely exonerate the cleansing agents and lay the blame squarely on the patient's psyche. The wide divergence of views among clinicians of experience emphasizes the need for careful objective studies of this disease of civilization, a social problem important as a source of disability and discomfort and of medico-legal controversy.

In his recent Watson Smith lecture, published in the opening pages of the *Journal* this week, Dr. F. Ray Bettley gives a valuable detailed survey of some of the effects of soap on the skin. His own experimental work[1 2] suggests that soap can facilitate penetration of the epidermal barrier by its own potentially irritating fatty acids and alkalis and by other substances. The incorporation of soap in barrier creams is therefore inadvisable. On the other hand the direct irritancy of soap has probably been exaggerated. True soap dermatitis is uncommon and presents as diffuse erythema and chapping. It is unlikely that soap is the primary cause of the nummular hand-eczema of housewives. The extent to which soap aggravates eczema is difficult to assess; it certainly appears to do so in some cases, but the wholesale prohibition of soap in all cases of eczema cannot be justified, for many will tolerate it well and the patients welcome the return towards social normality.

As the popularity of detergents for domestic use has increased rapidly since the war, so has the popular tendency to hold them, rather than soaps, responsible not only for cases of eczema of the hand but for generalized eczemas and for any eruption without an immediately obvious cause. Most of the commonly used detergents are of anionic type and are derived from petroleum, animal, or vegetable oils and sulphuric acid. They owe their detergent properties to the combination of a negatively charged lipophilic group and a positively charged hydrophilic group. Some 75% of the commercial product consists of "builder"—various sodium salts, carboxymethylcellulose, and fluorescent dyes. A report to the Committee on Cosmetics of the American Medical Association in 1957[3] emphasized the difficulty of assessing the cutaneous effects of detergents and reported an experiment in which immersion in a detergent solution 30 minutes twice daily failed to aggravate existing eczema of the hand. G. E. Morris[4] was unable to incriminate sensitization to soap or detergents in 57 cases of hand eczema, and he failed to produce irritation by immersion for 30 minutes in soap or detergent solutions at 105° F. (40.6° C.). Though it has been shown that certain detergents can denature surface horn, a recent investigation[5] found no correlation between the denaturing ability of domestic detergents and their effects on the skin. S. Rothman, whose brilliantly conceived studies have contributed largely to dermatological research, found with E. H. Ferguson[6] no convincing evidence from a review of the literature that detergents in reasonable concentrations damage the skin, and emphasized the importance of nervous factors in eczema of the hands.

[1] Bettley, F. R., and Donoghue, E., *Brit. J. Derm.*, 1960, **72**, 67.
[2] —— —— *Nature (Lond.)*, 1960, **185**, 17.
[3] Suskind, R. S., *J. Amer. med. Ass.*, 1957, **163**, 943.
[4] Morris, G. E., *Arch. Derm. (Chicago)*, 1955, **72**, 43.
[5] Harrold, S. P., *J. invest. Derm.*, 1959, **32**, 581.
[6] Ferguson, E. H., and Rothman, S., *Arch. Derm. (Chicago)*, 1959, **80**, 300.

Against this considerable weight of evidence tending to exonerate the soaps and detergents as frequent or important causes of eczema in the housewife must be balanced the firmly held convictions of many clinicians. The impartial critic is compelled to give the advantage to the defence. There is no doubt that in some cases soap and detergents can initiate or aggravate eczema of the hands particularly when these substances are used, as they often are, in concentrations many times greater than those recommended. But in most cases the unwarranted incrimination of these cleansing agents serves to distract attention from the actual causes and to discourage investigation. Eczema is a complex cutaneous reaction determined by the interaction of many factors. Metabolic and emotional factors modify the reaction threshold of the skin to external stimuli and potentiate their direct chemical or allergic effects. The eczematous changes once produced, their perpetuation may depend on the continued action of the initiating factors or on secondary infection, inappropriate treatment, or even an autoimmune mechanism. Every case of eczema of the hands requires careful individual assessment, and, though true cases of soap or detergent dermatitis undoubtedly occur, the hasty and uncritical application of this diagnosis can lead to the wrong advice being given.

DELIVERY BY SUCTION

Over 100 years ago Sir James Young Simpson[1] in Edinburgh was considering whether the application of suction to help delivery might be more effective than obstetric forceps. Little practical progress was made until recently, when T. Malmström, of Gothenburg in Sweden, devised his vacuum-extractor. His and other work was discussed in these columns last year,[2] when the hope was expressed that if the vacuum-extractor was being tried out in Great Britain a report on it would soon be forthcoming. Now at page 1684 of the *Journal* this week Mr. J. A. Chalmers and Dr. R. J. Fothergill give a full review of the pertinent literature and describe their experience with this instrument (which they prefer to call a ventouse). They used it on 100 women in labour, 79 of them primigravidae.

Basically the instrument consists of a suction cup attached by a chain, running inside a flexible rubber tube, to a metal traction handle, and connected to a vacuum pump and meter. The cup, which is made in three or four sizes, is applied to the foetal scalp and a vacuum, slowly increasing to 0.6–0.8 kg./sq. cm., is exerted. Traction is then applied perpendicular to the transverse axis of the cup intermittently in time with the uterine contractions. An artificial "caput" is thus raised on the part of the foetus, usually the vertex, to which the cup has been applied, but though the baby may look unsightly at birth the swelling soon abates and any damage to the scalp is minor and rare. Chalmers and Fothergill, however, still reserve judgment on whether the ventouse is safe for the extraction of the smaller premature babies. From the mother's point of view the advantages are that general anaesthesia is rarely required, that the instrument, unlike forceps, does not diminish the space available for the foetal head, and that excessive force detaches the suction cup before any damage can be inflicted on the birth canal.

In this Worcester series the chief indication for applying the instrument was prolongation of, or delay in, the second stage of labour. Indeed, one of the special merits here of the ventouse is said to be that, by applying it as far back as possible on the vertex, flexion of the foetal head is promoted and rotation of the head from arrest in the transverse or oblique diameters is naturally encouraged or can be artificially directed. Similarly a brow presentation may be flexed to become a vertex. Further, the ventouse was used successfully in three cases of breech presentation with delay in the second stage, the cup being applied to the anterior buttock. The second commonest indications were foetal or maternal distress, actual or pending. But if foetal distress was marked forceps were preferred as effecting delivery more quickly. Finally, the ventouse was used when, in the absence of disproportion, the first stage of labour was prolonged. It is claimed that cervical dilatation is thereby promoted "physiologically" by augmenting the uterine contractions as well as by drawing the presenting part down on to the cervical rim — an argument which will sound familiar to those who once used Willett's forceps similarly in cases of inertia and in deflexion of the foetal head.

One yardstick of the value of the ventouse in the series described was that in the first year of its use the forceps rate fell from 10.3% to 4.1%, the difference being accounted for by the employment of what the authors came to regard as a simpler and safer instrument. No doubt others will be stimulated to try out the vacuum-extractor in their hospital units, but it is also possible that eventually the ventouse may find some place in domiciliary practice.

EXERCISE THERAPY

The attitude to physical methods of treatment has changed during the past few years, and knowledge has advanced mainly as the result of the critical evaluation of techniques. Unfortunately discrimination in the prescription of physical methods of treatment is by no means universal, and in view of the prevailing severe shortage of qualified physiotherapists the country can ill afford the retention of ineffective techniques or the wastage of effort caused by the not uncommon use of these methods as placebos. N. Salter[1] has reviewed the principles underlying the proper use of exercise therapy.

It has always been known that suitable "training" begets an enhanced state of muscular efficiency, but only recently have we come to appreciate the nature of the many factors concerned in the achievement of this state. Because it is comparatively easily measured, muscle strength has been the criterion for most of the investigations carried out in this field, and there is no doubt that the strength and bulk of healthy muscle can be

[1] Simpson, J. Y., *Monthly J. med. Sci.*, 1849, **9**, 556.
[2] *Brit. med. J.*, 1959, **2**, 70.

[1] Salter, N., *Ann. phys. Med.*, 1957, **4**, 81.
[2] Lenman, J. A. R., *J. Neurol. Neurosurg. Psychiat.*, 1959, **22**, 182.

increased by active exercise and that the contralateral muscle also becomes stronger. The only way to increase muscle strength and endurance is by active voluntary movement. In therapy this may range from the employment of simple static contractions, through various methods of assisted movement with the elimination of gravity by the use of water, slings, or plane surfaces, to the use of the heaviest forms of resisted exercise which can be devised. The precise method used is probably immaterial so long as it is realized that requirements will differ from one patient to another and that exercise therapy is but one facet of the general management of the case. However, muscular strength and endurance are of little practical value without co-ordination, which depends on intricate physiological mechanisms and is correspondingly difficult to assess. Facilitation techniques aimed at increasing the degree of central excitation within the nervous system have recently become the subject of some interest, and either alone or in combination with progressive resistance exercises may produce beneficial results in a wider group of disorders than could otherwise be influenced.

Exercise therapy produces the most obviously satisfactory results in cases of simple disuse atrophy, because only normal muscle with an intact nerve supply is present. Good results are also obtained when recovery from denervation is taking place, and also after poliomyelitis, when suitable exercises may lead to a more rapid recovery in the remaining intact neurones. The application of exercise techniques to the treatment of the rheumatic diseases requires much judgment because the wasted muscles cannot be divorced from the diseased joints, misuse of which will increase pain and muscular inhibition, and because in some cases the muscle itself is affected by the disease process.

J. A. R. Lenman[2] has recently made a scientific appraisal of the effects of exercise on motor weakness in certain types of neurological disease. In cases of muscular dystrophy it was possible to increase muscle strength, albeit very much more slowly than in normal muscles, but the progress of the disease tended to neutralize any improvement which occurred. In cases of motor-neurone disease the appearance of fasciculation did not necessarily indicate an increased rate of destruction of anterior horn cells, and fatigue was not found to cause any adverse effects. But though increased strength was noted in some of the muscles exercised, it seemed that the sole effect of exercise in these cases was due to the correction of wasting caused by disuse. The day-to-day fluctuations in muscle strength so characteristic of disseminated sclerosis tend to make the assessment of treatment difficult, but Lenman noted a significant increase in strength after exercise only when remission was occurring. In poliomyelitis and certain forms of neuropathy Lenman confirms that, once recovery has begun, it can be hastened by exercise. It appears that exercise has an important but restricted part to play in the management of neurological disease, particularly in the prevention of stiffness and the correction of weakness due to disuse in comparatively unaffected muscles.

Amid the very proper concern for the critical evaluation of techniques the psychological aspects of therapeutic exercise should not be overlooked. The patient's co-operation can be achieved more easily if the form of exercise is interesting, and particularly if there is an end product of some sort. Skilled assessment of individual needs is often required.

DEPTH IN MICROSCOPY

The optical microscope has a very small depth of field, so that only a thin "optical section" of the object can be seen at a given level of focus. The electron microscope, on the other hand, has a very large depth of field, so that everything throughout the thickness of the specimen can be photographed simultaneously on one plane. In neither case is it possible to deduce the exact three-dimensional structure without the laborious use of serial sections. The binocular stereoscopic microscope provides an impression of depth, but the actual depth of field is only the same as that given by an ordinary optical microscope.

One solution to the problem is to focus up and down rapidly through the specimen at such a rate that successive optical sections are presented almost simultaneously to the eye. A prototype instrument along these lines has been constructed by Mr. Richard Gregory at the Psychological Laboratory, Cambridge, with the aid of a grant from the Department of Scientific and Industrial Research. The objective lens is supported on a bar which rests on two electrically operated vibrators. An image is projected on to a small screen attached to an electrically controlled tuning-fork. The relative phases of vibration of the objective and screen are adjusted by means of an electronic device so that the image screen moves synchronously with the objective, but with a greater amplitude. In this way a solid image of the specimen is built up in the volume swept by the moving screen. The instrument is rather cumbersome in its present form and has been used only with low-power lenses. It might be possible to simplify it, particularly if some auxiliary optical component, rather than the objective itself, were vibrated. Unfortunately the contrast is inherently low, because each image plane is seen against an illuminated background, and in any case there is bound to be considerable scattering of light in a thick specimen. Problems of contrast are likely to become more serious at higher magnification.

A successful instrument of this type would certainly be most valuable for looking at thick histological sections and for studying complex cellular interrelationships such as occur in neurology. The possibility of following processes such as cell division in three-dimensions is also stimulating. While the solution of the many technical difficulties encountered is not yet within sight, the end is so well worth while that further work should be encouraged.

We record with regret the death on May 29 of Professor John Fulton, Sterling professor of the history of medicine at Yale University.

Drug Treatment of Disease

INTRACTABLE PAIN

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The challenge of pain has been accepted and met by doctors for centuries, and throughout many long illnesses both they and their patients have had reason to bless pain-killing drugs. The treatment of intractable pain may seem to be a contradiction in terms, but common usage supports the *Shorter Oxford English Dictionary* (1933) definition of such pain as "stubborn," "refractory," and "not easily treated." It may vary from obstinate, sullen discomfort to excruciating torment.

Severe pain occurs at times in three main groups of patients—firstly, in comparatively short-term, self-limiting conditions such as fractures, burns, and war wounds, incipient gangrene, and after certain operations; secondly, in a longer-term group of illnesses, with which patients must learn to live, such as rheumatoid and osteo-arthritis, post-herpetic neuralgia, and chronic pancreatitis; and thirdly in fatal diseases such as carcinomatosis, with invasion of nerves or pressure on them by malignant growth, particularly in the spine and pelvis.

The attitude towards intractable pain adopted by a patient and his relatives, his doctor and nurse, will depend to some extent on the group into which his illness falls, especially when morphine and morphine-like drugs are being considered and the possibilities of tolerance and addiction have to be borne in mind. But whenever such pain develops, and whatever its cause, its relief helps not only the patient but all who have to see him suffer; and the success of its treatment may be a major factor in maintaining morale wherever the patient is being nursed.

The experience of general practitioners, expressed in the number of patients in severe pain being treated at any one time, must be less than that of many other observers; but the closeness of a family doctor's contact with his patients throughout long illnesses, accidents, or major operations, and the fact that he is often left responsible for terminal care when the hospital can do no more, may give him knowledge of pain-killing drugs which is difficult to gain elsewhere.

Our concern in this paper is with the drugs used for the symptomatic treatment of pain itself, not with those which modify or remove its cause, as chemotherapy may do in infections, hormones or nitrogen mustard in certain cancers, or as colchicum does in gout. We shall not discuss those used for surface anaesthesia, for local or regional anaesthesia by injection, or those for general anaesthesia. We shall mention the approved pharmacopoeial name of each drug and not more than two trade names—those we know best.

Some General and Nursing Points

As family doctors we have often had to help patients through long, formidable, and even terrible illnesses; and we have been impressed, as so many have been before, by the different reactions to pain shown by different patients, or by the same patient under different conditions of interest, excitement, exhaustion, or disease. Some sixty years ago Sir Lauder Brunton wrote: "A local injury which a man in health would scarcely heed or would indeed hardly feel may cause the same man, when broken down by illness, to feel the pain most acutely and express his feelings in terms which those around him think exaggerated." We have been impressed, too, by the benefits which may be gained by mixing analgesics, by changing them from time to time to minimize sensitivity, tolerance, or addiction, and by the occasional severity of withdrawal symptoms when one powerful drug is replaced by another in doses which are not of equivalent potency. Such withdrawal symptoms may easily be mistaken for toxic effects from the new drug.

It is easier to prevent the onset of pain than to alleviate it once it is there, so that analgesics are most effective when given before attacks of pain are fully developed. A patient in pain should not have to watch the clock and count the minutes until his next injection is due. Much annoyance and apprehension in patients and onlookers may be caused by unnecessary delay in bringing relief, and they may be comforted by knowing that a tablet is put out, or a syringe loaded near by, ready to help at once should a spasm of pain come on. Special instruction of the nursing staff on these matters may be needed. A pain chart indicating the time, severity, and duration of each attack, kept by a nurse and never mentioned or shown to the patient, is sometimes a help.

We are convinced of the value of mild analgesics, given regularly, for the pains suffered by patients with early arthritis, prolapsed intervertebral disk, Paget's disease, etc., and of their help as background therapy in more severe cases to reduce the dose of stronger drugs. We shall mention first these milder analgesics, with the potentiating or reinforcing agents which are so useful in treating pain, before discussing more fully the use of morphine and synthetic morphine-like drugs and their antagonists.

SALICYLATE AND ANTIPYRETIC GROUP OF ANALGESICS

The milder analgesics are nearly all of the salicylate and antipyretic group. Those we find most useful clinically, at present, are given below, with the analgesic dose approximately equivalent to 10 gr. (600 mg.) of aspirin.

Drug	*Dose Approximately Equivalent to Aspirin (10 gr.) in Analgesic Effect*
Acetylsalicylic acid (aspirin)	600 mg. (10 gr.)
Phenacetin	600 mg. (10 gr.)
Phenylbutazone ("butazolidin")	100 mg. (1½ gr.)
Salicylamide ("salimed")	1 g. (15 gr.)
Paracetamol ("panadol," "tabalgin")	1 g. (15 gr.)

All these mild analgesics are taken by mouth and, because of their brief action, frequent doses are often necessary, perhaps every two or three hours, to maintain continuing analgesia. Some of them irritate the mucous membrane of the stomach, occasionally causing erosion, haematemesis, or melaena. These dangers are reduced but not altogether eliminated by giving them crushed into powder taken with a glass of water, on a full stomach, or by prescribing them with sodium bicarbonate, in emulsion, or as soluble aspirin (" disprin " or " solprin " brands of calcium aspirin). Alternatively they may be buffered with aluminium glycinate and magnesium carbonate (" bufferin "), with glycine (" paynocil " and other so-called flash-dispersal tablets), or with aluminium hydroxide (" alasil "). Enteric-coated aspirin tablets (" enseals," recently replaced by " nu-seals ") prevent this mucosal ulceration of the stomach altogether, but they may slow the rate of absorption. When aspirin is prescribed with sodium bicarbonate its renal excretion is accelerated and larger or more frequent doses may have to be given. After an overdose the most usual symptoms of salicylism are nausea, vomiting, tinnitus, and deafness.

Alternatives to Aspirin

When pain occurs in those who are allergic to aspirin, or in asthmatics, any of the other members of this group of drugs may be helpful. Phenacetin and salicylamide damage the gastric mucosa much less than does aspirin, but occasional ill-effects from the former include methaemoglobinaemia, haemolysis, and renal damage. Paracetamol seems, in our experience, gradually to be replacing phenacetin and salicylamide.

Phenylbutazone, though it has sometimes caused agranulocytosis or aplastic anaemia, may be given with comparative confidence in doses of 100 mg. four times a day. We have found it very useful; but care should be taken with those patients who give a history of peptic ulcer, liver or kidney disease, or of blood dyscrasia after taking other drugs. The patient should be warned to report any sore mouth or throat, fever, nausea, vomiting, indigestion, or diarrhoea, and watch must be kept for bruises, skin rashes, and fluid retention. After a precautionary initial blood count, repeated white-cell counts are not usually helpful; they may even lead to a sense of false security, for a drop in the granulocyte count may be sudden and unpredictable and, if a recent blood count has been normal, the correct diagnosis may not even be suspected. Patients who show gastric intolerance of this drug may be given it intramuscularly (with procaine to minimize the pain of the injection), or in a suppository (250 mg.).

These mild analgesics are now sold under a great variety of trade names and in a remarkable and bewildering series of mixtures—often several together in a tablet with vitamins, tranquillizers, sedatives, hypnotics, stimulants, antispasmodics, stronger analgesics, laxatives, iodine, and even with steroids. Many of these mixtures are popular and helpful such as tab. codein. co., or " veganin " tablets which contain a little more codeine. When prescribed with caffeine (in the well known A.P.C. mixture, or as " anadin ") or with amphetamine, they must not be given in the evening or at night. We have seen many patients whose rest has been sadly disturbed because they have not appreciated that their " pain tablets " contained a stimulant expressly to keep them awake.

POTENTIATING DRUGS FOR ANALGESIA

Among the most helpful potentiating drugs for reinforcing analgesics are promazine (" sparine ") and chlorpromazine (" largactil ") in doses of 25 to 75 mg. six-hourly by mouth. Other sedatives and tranquillizers —from phenobarbitone (" luminal," " gardenal ") to meprobamate (" equanil "), amylobarbitone sodium (" sodium amytal "), or hyoscine—are sometimes useful adjuvants too; they raise the level of pain acceptance, and enable patients to bear more stoically an otherwise intolerable discomfort. Cocaine hydrochloride, amphetamine, dexamphetamine, steroids, cannabis indica, and other euphoriants may be helpful for the same reason. Adequate sleep is always important and additional hypnotics are often needed. No one understood this better than John Hilton (1863), who, in his lectures on rest and pain 100 years ago, spoke of " Pain the monitor, and rest the cure."

Alcohol

Alcohol—possibly the oldest analgesic of all—deserves a paragraph of its own. Its pain-killing and euphoric properties have probably been recognized for tens of thousands of years. It is one of the few substances which are absorbed from the stomach itself, so that it acts quickly; and it has been included in many analgesic potions, as in the famous original Brompton Hospital " cocktail "—morphine hydrochloride $\frac{1}{4}$ gr. (15 mg.), cocaine hydrochloride $\frac{1}{6}$ gr. (10 mg.), gin 60 minims (4 ml.), honey 60 minims (4 ml.), chloroform water to $\frac{1}{2}$ fl. oz. (15 ml.). In many terminal illnesses the possibility of alcohol helping to relieve pain, in a suitable person, can usefully be borne in mind; large amounts may be needed to produce an effect in those who are accustomed to it. Its vasodilating qualities are useful when treating the pain of peripheral vascular conditions; but in Hodgkin's disease and other lymphomas it may even cause pain. Chronic alcoholism is always a danger when a patient (especially a young man or girl) starts taking spirits " as a medicine " to relieve discomfort.

MORPHINE AND MORPHINE-LIKE DRUGS

Where pain is concerned there are major difficulties in carrying out controlled experiments in clinical pharmacology and therapeutics. Doctors cannot yet agree on the relative merits of even those members of the opium group of analgesics which they have known the longest: the recent heated controversy and division of medical opinion when the ban on heroin was contemplated illustrated this only too well. How much harder will it be to assess accurately the relative pain-killing qualities of the newer synthetic compounds which are appearing on the market in increasing numbers, and whose therapeutic efficacy depends so much on individual variations and sensitivities, methods of prescribing, and on rates of absorption, destruction, or excretion. The frequency and severity of side-effects fix a ceiling for the dosage of each (Nathan, 1952).

Instead of attempting to judge these new preparations too critically, on inadequate evidence, a more useful purpose will probably be served in a paper such as this by mentioning their approved pharmacopoeial names and trade names, and, as morphine is the yardstick by which their analgesic effects are measured, by giving against each as a rough clinical guide the analgesic dose approximately equivalent to 10 mg. (1/6 gr.) of

morphine. We shall then consider in a general way their prescription for the treatment of intractable pain, the advantages which are claimed for each, and any undesirable features which have so far been noted.

We appreciate the risks of oversimplification in a short discussion of so complicated a subject as this. In the search for new analgesics more than 200 morphine-like substances had been synthesized even by 1955, only a few of which have proved to be of real value (Eddy, 1956). As John Morley (1931) wrote, "The issue must be decided in the last resort, not by claims to greater simplicity, but by the test of clinical experience."

Drug	*Dose Approximately Equivalent to Morphine (1/6 gr.) in Analgesic Effect*
Morphine sulphate	10 mg. (1/6 gr.)
Papaveretum (mixed alkaloids of opium) ("omnopon, opoidine")	20 mg. (1/3 gr.)
"nepenthe"	1.2 ml. (20 minims)
Codeine phosphate	60 mg. (1 gr.)
Diamorphine hydrochloride (heroin)	5 mg. (1/12 gr.)
Pethidine hydrochloride	120 mg. (2 gr.)
Dihydromorphinone hydrochloride ("dilaudid")	2 mg. (1/32 gr.)
Methadone (amidone, "physeptone")	10 mg. (1/6 gr.)
Dipipanone hydrochloride ("pipadone")	25 mg. (2/5 gr.)
Levorphanol tartrate ("dromoran")	2 mg. (1/32 gr.)
Oxycodone pectinate ("proladone")	10 mg. (1/6 gr.)
Dihydrocodeine bitartrate ("D.F.118")	50 mg. (¾ gr.)
Phenadoxone hydrochloride ("heptalgin")	10 mg. (1/6 gr.)
Dextromoramide ("palfium")	5 mg. (1/12 gr.)
Phenazocine ("narphen")	2 mg. (1/32 gr.)

Codeine

As an analgesic drug of medium potency codeine is sometimes useful in doses of 30–60 mg. (½–1 gr.). In the past it has too often been prescribed in insufficient amounts. It does not depress the respiratory centre to the same extent as does morphine, it causes less nausea and constipation, and it is less hypnotic; but all these side-effects may be troublesome with larger doses. Addiction is so rare that it is not subject to D.D.A. regulations. The small amount of codeine in tab. codeine co. (8 mg., ⅛ gr.) has hardly any additive analgesic action.

Morphine

Most clinicians and pharmacologists agree that "Morphia is still the most efficacious remedy for severe pain, and it is the most widely used of the strong analgesic drugs. It is the 'yard-stick' with which many are compared" (Roberts, 1959). This opinion is endorsed by Professor F. H. Shaw, of Melbourne, who has reported with his associates more than five years' experience based on six hundred patients suffering from carcinoma, and who has carried out experiments on over a hundred volunteers (Moon and Shaw, 1960; Shaw, 1960). J. Cameron Morris (1959), in charge of 48 beds at St. Luke's Hospital for the Dying, said last year, "We try the new analgesics as they come out; but nearly always, sooner or later, we come back to the old stand-bys—nepenthe by mouth, morphine by injection." Several of the lessons about analgesics learned in treating malignant disease can be applied, with reservations, elsewhere.

The popular misconception that the most powerful analgesics of the morphine group are so dangerous that they should be given only in the last resort is sometimes an unfortunate hindrance to the adequate relief of pain. The objective must be complete and continuing freedom from severe pain, not merely temporary relief with the drugs being given only when pain has returned. When morphine is administered in appropriate combination with its antagonists, as discussed later, complete analgesia can often be both safe and pleasant; apprehension, fear, and distress are greatly reduced, and the patient can continue on these mixtures for many months.

Side-effects of Morphine

The immediate danger after a dose of morphine is its liability to cause depression of the respiratory centre. Though this happens less often than was at one time thought, large initial doses and intravenous injections of this drug are best avoided except under special circumstances (see later). A slow respiration rate of six breaths a minute may give adequate ventilation and be quite safe so long as each breath is deep. When large doses of morphine are needed to stop pain, however, as after a severe accident, war wound, or operation, careful watch must be kept for shallowness of respiration and cyanosis; and the greatest care must be taken in cases of head injury and when there is increased intracranial tension, in chest injuries, in asthmatics (in whom it may also increase bronchospasm), and in infants and the aged whose respiratory centres are particularly susceptible to this drug.

Other unpleasant side-effects from morphine which have limited its use in the past, especially in patients who have been over-sensitive to it, have been nausea and vomiting (beginning perhaps four to seven hours after the injection), dizziness or light-headedness ("I feel dopy")—all worse when the patient is up and about—constipation, retention of urine, sweating, drowsiness, unusual dreaming, dulling of the intellect, mental confusion and disorientation or hallucinations, especially in the elderly. In rare cases allergy to the drug develops with itching, urticaria, or other rashes. Even with modern combined therapy all these distressing side-effects have to be taken into careful account, though they can now largely be overcome by simultaneous administration of the so-called antagonists to morphine, some of which, in therapeutic doses, do not counteract its analgesic properties. Without these antagonists, side-effects give rise to trouble in about one-third of all patients treated with morphine, which is why some doctors in the past have not been enthusiastic about using it, and why the search for new analgesics has gone steadily on.

Tolerance to morphine does develop, but not always as quickly or as seriously as was at one time supposed. It is a long-term inconvenience rather than a danger. During short painful illnesses the problem of tolerance hardly ever arises, and even in those which last two months or so only a comparatively small increase in dose may be needed. Tolerance to side-effects does not always keep in step with tolerance to analgesia. Cross-tolerance may develop between different analgesics (Dundee, 1960).

Addiction to Morphine

The length of time that morphine has to be given before addiction sets in varies a great deal; it is usually several weeks. In the past a fear of addiction often discouraged doctors from making the best use of morphine when treating patients with intractable pain. Nowadays addiction is rare if the drug is properly used, and objection to it because of this danger is not justified

in short painful illnesses, after accidents or operations, or in conditions which are likely to prove fatal. Rather than allow a dying patient to suffer continuing discomfort for months, perhaps his last few months, how much better to give him relief without being niggardly or over-cautious, and to prescribe an adequate dose of the drug to keep him comfortable and happy—even though this may mean a larger daily dose than is usually given, and keeping it up until his death to avoid withdrawal symptoms.

In young and middle-aged patients, however, with chronic painful illnesses with which they will have to live for many years, the danger of addiction to morphine is still a real one and the greatest care should be taken to avoid it. The old rule of thumb—that it is unwise to prescribe morphine for long unless the end of a painful illness can be foreseen either in recovery or death—still holds. Many doctors would feel worse about being responsible for producing one addict than for failing to relieve pain entirely in a chronic condition. Particular care must be taken with young people who have easy access to the drug, such as nurses, medical students, and pharmacists, who may start taking it for dysmenorrhoea or migraine. Addiction is now thought by many to depend as much on psychogenic factors as on the amount of morphine which is taken or the length of time over which it is given.

There is some evidence that when morphine is prescribed with its antagonists addiction is less likely to arise than when it is given alone, and that it can be withdrawn more quickly without deprivation symptoms. This needs confirmation. In our small experience with this type of case, a confirmed addict with physical and emotional dependence on the drug will not always readily accept combined treatment.

Deprivation symptoms may begin to show themselves five to ten hours after withdrawal of the drug, are usually of maximum intensity about four days later, and may last for one or two weeks. They include yawning, running at the eyes and nose, sweating, restlessness and irritability, insomnia, depression, tremors and twitchings, nausea, vomiting, and sometimes diarrhoea and dehydration.

Administration of Morphine in Short Illnesses and after Accidents or Operations

Many patients are remarkably free from pain during severe illnesses, after fractures and other accidents, war wounds, and surgical operations. They need no analgesic drugs, and in fact do better without them. When pain is severe, however, it can often be completely controlled by morphine, whose dangers and undesirable side-effects may be reduced to a minimum by giving it in the following way.

At first 10 mg. (1/6 gr.), for an average-sized adult, is injected subcutaneously or intramuscularly. Some relief should be noticed by the patient in ten minutes; it should be maximum in twenty or thirty minutes and should last four to six hours. If the pain does not disappear entirely with this first injection, it may be repeated in one or two hours; any troublesome side-effects, should they occur, being counteracted in the ways set out in the next few paragraphs. The dose may be repeated every six or eight hours; if pain persists, it may be increased half as much again at each injection until there is complete freedom from pain with three or four injections every 24 hours.

After an operation, if severe pain is expected, the first dose of morphine may be given before the pain is at its height. This often reduces the total amount which is needed to keep the patient comfortable.

After severe accidents, some major operations or war wounds, and in other conditions of shock, when the peripheral circulation is poor and the blood-pressure low, the drug may be absorbed slowly, its analgesic effect may be delayed, and large or repeated doses (the time being carefully recorded as they are given) may be needed to kill pain. It will then act for longer than usual, and one must bear in mind that, if the blood-pressure rises rapidly to normal a little later, absorption of all that has been injected may take place at once and signs of an overdose may appear. Under these conditions special watch must be kept on the respiration rate and depth of sedation. Whenever for these reasons absorption from subcutaneous tissue or from muscle is likely to be slow, there is a place for the intravenous administration of morphine; but a smaller dose than usual will then be needed and the injection must be given slowly, for respiratory depression may occur.

A most important consideration in general practice is that it may often be difficult or impossible for family doctors or district nurses to inject a patient frequently or at regular intervals in his home. It is for this reason that the preparations of the alkaloids of opium which are given by mouth are so popular—papaveretum (omnopon, opoidine) and nepenthe. They owe their pain-killing action almost entirely to the morphine they contain (omnopon 50% anhydrous morphine, nepenthe 0.84%); the additive effect of the other alkaloids in them is small. Suppositories containing morphine are useful for a more gradual and prolonged effect. On occasions "tubunic ampoules" of omnopon (15 mg., ¼ gr.) or "ampins" of morphine may be helpful; they enable a competent and reliable layman to give an injection in an emergency.

Treatment of Side-effects of Morphine

Respiratory Depression.—After the first few doses of morphine, and after any large dose (especially if barbiturates are being taken at the same time), careful watch must be kept for undue slowing of the respiration rate and for cyanosis, and the airway must be kept clear. If slight respiratory depression occurs, an analeptic, or stimulant of the central nervous system, such as nikethamide ("coramine"), leptazol ("cardiazol"), or amiphenazole ("daptazole") should be given intramuscularly or intravenously. A recent promising development in Australia (Moon and Shaw, 1960; Shaw, 1960) has been the use of tetrahydroaminacrin ("tacrine" or "T.H.A."). It has some advantages over amiphenazole (see below), and we understand that it will soon be available in Great Britain.

If respiratory depression from morphine is severe enough to threaten life, its complete antagonists will be needed—nalorphine ("lethidrone") or levallorphan tartrate ("lorfan") (see later, under treatment of overdose). When morphine is given repeatedly the respiratory centre soon becomes tolerant to it, even to large doses.

Nausea and Vomiting.—These limit the use of morphine more than any other side-effects. They are best prevented, or treated if they occur, by promazine, chlorpromazine, cyclizine ("marzine"), dimenhydrinate ("dramamine") by mouth or intramuscularly (all 25-

50 mg.), or by promethazine chlorotheophyllinate ("avomine") by mouth (25–50 mg.), repeated as required.

Constipation.—The constipating effect of morphine is relieved by laxatives. The importance of adequate fluid intake should never be forgotten.

Drowsiness.—Mild drowsiness may be helped by stimulants such as caffeine, amphetamine ("benzedrine"), or dexamphetamine sulphate ("dexedrine"), which are useful when a patient who is taking an analgesic wishes to keep awake and to work during the day. Amiphenazole (in doses of 20–100 mg. six-hourly, usual dose 30 mg.), or tetrahydroaminacrin (10–15 mg.), may also counteract this narcotic action: they can be given by mouth, or subcutaneously or intramuscularly in the same syringe as the morphine. Amiphenazole is a powder and remains stable in solution for only 24 hours at room temperature or for seven days in a refrigerator. In this respect tetrahydroaminacrin is more satisfactory; being more stable in solution it can be supplied in the same ampoule as morphine. We have had some good results from a combination of morphine and nalorphine. All these stimulants should be omitted or reduced during the night, so as not to upset the patient's sleep. If their effects persist after bedtime a hypnotic may be needed.

Mental Confusion, Hallucinations, etc. — Mental confusion from morphine, especially in the elderly, probably means that another analgesic should be tried such as pethidine or heroin, or better still oxycodone pectinate. In the past hyoscine has been a favourite remedy for this side-effect.

Administration of Morphine in Long Illnesses Likely to Prove Fatal

In patients with inoperable cancer or other formidable painful illnesses, for whom treatment may last a year or more, tolerance to morphine will almost certainly develop, and an increase in dose of 15 mg. (¼ gr.) may be required every two months or so. The size of this increase and the time at which it is needed vary, of course, considerably. Doses of morphine up to 130 to 200 mg. (2 to 3 gr.) six-hourly may occasionally be required. To counteract drowsiness during the day stimulants may be given with each injection (in the same syringe as the morphine) or by mouth. The dose of stimulant required is not directly related to the dose of morphine; it is adjusted to produce the right degree of alertness. Nausea and vomiting may sometimes be troublesome, too, and need counteracting as already described; though patients who have received morphine for some time develop considerable tolerance to these symptoms, as they do to respiratory depression. Larger doses of morphine than this, or more frequent injections, are seldom needed, but isolated cases have been described which required enormous amounts. It is well to remember that in any patient who is receiving morphine continuously an abdominal emergency may easily be missed.

Up to a point morphine induces a sense of tranquillity and detachment, "a feeling of release and thankfulness" as one patient described his experience to us recently; but during long-drawn-out painful illnesses some patients not unnaturally become depressed. The addition of stimulants helps to banish lassitude and persistent sleepiness, as well as this depression, all of which can be distressing to the patient and troublesome from a nursing point of view when seriously ill people in pain are being treated with large doses of morphine. It is a great help to have such patients alert and co-operative with an interest in life, in their hobbies, and in people and things around them; better still if they can be up and about, sitting out of bed or even out of doors, reading, talking, knitting, or taking part in organized occupational therapy. Some indeed may develop too much insight into their medical condition, and when this happens the dose of stimulant is best reduced. At the end of a long illness, as death approaches, all stimulants can be omitted and drowsiness encouraged.

Treatment of Overdose of Morphine

Chronic overdosage with morphine, with all its side-effects, has often, in the past, left patients in a pitiable state of cachexia and demoralization. With an adequate diet, correct dosage, and modern combined treatment this is less likely, and physical or mental deterioration should now occur less frequently from the use of this drug.

A large single overdose, with danger to life, is best treated with morphine's complete antagonist—nalorphine—which counteracts all its effects, including most of its analgesic action (this depending on the dose), and can produce withdrawal symptoms. 10 mg. (1/6 gr.) may be given intravenously, repeated more than once if necessary. Its action is somewhat transient compared with that of morphine, so that the possibility of a relapse must be remembered; if this happens treatment with nalorphine can be continued intramuscularly or subcutaneously. Levallorphan tartrate is another potent antagonist. Every effort must be made throughout to keep the airway clear.

Synthetic Morphine-like Drugs

All the synthetic morphine-like drugs listed above (p. 1725) are useful at times for the treatment of intractable pain, especially in patients who are sensitive to morphine in one way or another. They can all be taken by mouth more satisfactorily than can morphine, which is of great importance in general practice. The claims of the pharmaceutical firms who make them that their side-effects are fewer than those of morphine, that tolerance develops less easily, and that addiction is less likely to occur, are difficult to confirm by clinical trials because they are so often prescribed in doses which are not equi-analgesic to large doses of morphine, and some have not yet been long enough in routine use.

As with morphine, the action of all these synthetic drugs is likely to be unduly prolonged in patients with liver or kidney disease, when smaller doses may be needed. They are nearly all subject to D.D.A. regulations. Everything that has been said in this paper about morphine, its side-effects and their treatment, tolerance and addiction, and its use in short-term and long-term illnesses, applies also in some degree to heroin, pethidine, and all these other synthetic compounds.

When for any reason one of these synthetic drugs is thought to be preferable to morphine for treatment of an intractable pain, it may be tried first, and if it does not prove effective in controlling the pain entirely when given in regular doses a change-over to morphine or another preparation can easily be made. When taken by mouth the best time for maximum absorption is just before meals; but even then results may be inconsistent,

for the effect depends on how quickly the stomach empties, as these drugs are not absorbed from the stomach itself. They may also be given subcutaneously or intramuscularly, and occasionally intravenously (in half doses) when a rapid result is wanted as in the presence of shock. Some are put up as suppositories (dilaudid, proladone, palfium). The drugs of medium potency, such as dihydrocodeine bitartrate, usually need four-hourly rather than six-hourly injections when pain is bad. In infants and old people, after chest and head injuries, and in asthma, it is wise, as with morphine, to give half the usual dose at first. All the morphine antagonists counteract the effect of these synthetic morphine-like drugs to a greater or lesser extent. The analgesic and its antagonist are sometimes prescribed together, as in the proprietary preparation "pethilorfan" (2-ml. ampoules containing 100 mg. pethidine and 1.25 mg. lorfan), which reduces side-effects. The treatment of overdose for all these synthetic preparations is the same as that for morphine.

Diamorphine hydrochloride (heroin).—Some pharmacologists believe that heroin is even more liable than morphine to cause addiction, and for this reason it is no longer included in the *British Pharmacopoeia*. It depresses the respiratory centre more than morphine, but it less frequently causes nausea and vomiting. It gives some ill patients a more benign mental outlook and makes them easier to manage. Of such cases it has been well said that heroin is a "kinder" drug than morphine.

Pethidine hydrochloride has been gaining steadily in popularity during the last few years and is replacing morphine for many purposes; but for the treatment of severe intractable pain the general opinion is that neither pethidine nor these other synthetic preparations are really as effective pain-killers or as reliable as morphine, though pethidine depresses the respiratory centre less. We have sometimes found it valuable when nausea, vomiting or mental confusion from morphine have been troublesome; but it can itself sometimes produce these same side-effects. Pethidine is liable to cause an addiction almost as severe as that of morphine. It is said to have more spasmolytic action than others of this group except in the biliary and renal tracts, where, like morphine, it may precipitate spasm rather than relieve it. When treating renal, biliary, or intestinal colic, we use it with atropine and find this combination most helpful. The solubility of pethidine is comparatively poor—an injection of at least 2 ml. being required for every 100 mg. given—which is a disadvantage at times, especially in emaciated patients who need large doses.

Dihydromorphinone hydrochloride (dilaudid) is less liable than morphine to cause nausea, vomiting, constipation, and drowsiness. The duration of its action is shorter, however, and the need for more frequent doses has disadvantages.

Methadone (physeptone), also, is less hypnotic than morphine and is therefore useful during the day. We have used it satisfactorily in ambulatory patients, though this is not recommended by its makers because of possible side-effects. It is well absorbed by mouth, is not unduly constipating, and is suitable for moderately severe pain. With its spasmolytic action it is useful in the treatment of colic.

Dipipanone hydrochloride (pipadone) has more hypnotic effect and causes less respiratory depression than morphine. It is particularly useful after operations (Cope and Jones, 1959). 25 mg. in combination with 50 mg. cyclizine as a compound tablet is especially effective.

Levorphanol tartrate (dromoram) is longer-acting than morphine and has less hypnotic effect. It is suitable for daytime use, when its analgesic action may last for as long as eight hours. It is as effective by mouth as by injection if absorbed quickly. Its undesirable reactions are less than those of morphine, but ambulatory patients may complain of dizziness and nausea at the beginning of treatment.

Oxycodone pectinate (proladone) is also long-acting, causes less mental confusion in the elderly than does morphine, and is often useful for this reason. It has less euphoric effect and is a useful substitute when dependence on morphine or pethidine is feared.

Dihydrocodeine bitartrate (D.F.118) is one of the weaker drugs of this group, with an action of comparatively short duration. It is exempt from D.D.A. regulations at present.

Phenadoxone hydrochloride (heptalgin) is another of weaker potency, but with a marked spasmolytic effect. Some observers have found it unreliable by mouth and unpleasant by injection (Nathan, 1952).

Dextromoramide (palfium) is a strong analgesic with a rapid action, and is less likely to cause drowsiness and constipation than morphine. Some surgeons have given up using it in post-operative cases because of its liability to cause respiratory depression (Cope and Jones, 1959). For this reason care must be taken when prescribing it with barbiturates at night, which should be given in half doses.

Phenazocine (narphen) is a new preparation of which there have been good reports. It is said to have fewer undesirable side-effects than morphine and a longer action.

Conclusion

In this discussion on the treatment of intractable pain with drugs the chief analgesics have been considered separately, though in practice it happens almost invariably that patients receive mixtures of them, given together or at different times of the day or night. These mixtures are extremely helpful.

Every doctor has his favourite prescriptions for treating continuing pain. Ours at present are: aspirin, phenylbutazone, and paracetamol in the salicylate and antipyretic group of milder analgesics; codeine and methadone in the group of intermediate strength; and morphine, pethidine, heroin, and levorphanol, in the strongest group.

With so many from which to choose we are prepared to change to others at once when we are convinced that they are better than those which help us most now. Clinical impressions of the value of new pain-killing drugs are often fairly clear from personal experience, but scientifically accurate comparisons are difficult to make under the conditions of general practice. The ultimate test for a family doctor often proves to be what happens to suit one particular patient best.

Morphine, though not the best analgesic for every person in severe pain, still seems to be the most reliable and effective drug for the majority, when conditions are suitable for its use. The addition of its various antagonists to the pharmacopoeia has made its administration in large doses much safer and less unpleasant for patients; which makes even more true to-day than

in the past the old aphorism that "morphia exists to be given, not merely to be withheld."

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MASS IMMUNIZATION WITH LIVE POLIOVIRUS VACCINE IN THE SOVIET UNION

[FROM A SPECIAL CORRESPONDENT]

At a scientific conference on live poliovirus vaccine held in Moscow from May 17 to 20 the progress of the work on the mass immunization of the population of the U.S.S.R. was reported. Immunization against poliomyelitis by the use of the Sabin live, attenuated, poliovirus vaccine began in the Soviet Union in 1957–8. Professor Smorodintsev and his colleagues of the Leningrad Institute of Experimental Medicine showed that the feeding of the Sabin vaccine to 1,200 infants produced no untoward reactions, and that the vaccine viruses, after a series of consecutive passages in polio-antibody-free children, showed no major increase in their neurovirulence for monkeys. As a result of these observations a larger immunization programme was carried out from January to April, 1959, under the direction of Professor Smorodintsev and Professor Chumakov, of the Institute for Poliomyelitis Research, Moscow. The programme involved the feeding of 27,000 children in Estonia and Lithuania with vaccine provided by Dr. Sabin, and of 12,000 children in Latvia with vaccine prepared in Leningrad. The result of this programme led to the conclusion that the vaccine was entirely safe, and it was therefore decided to extend the vaccination programme using only vaccine made in the Soviet Union. Preparation of the vaccine was begun on a large scale at the Institute for Poliomyelitis Research, and by June, 1959, more than three million people—mainly between 2 months and 20 years of age—were vaccinated in Estonia, Lithuania, Latvia, and a number of other areas. By the end of the year vaccination was in progress in all except one of the Soviet Republics, and more than 15 million people had received the vaccine.

55 Million Vaccinated

The next stage in what can only be described as this *Blitzkrieg* against poliomyelitis was the decision to vaccinate all persons in the U.S.S.R. between the ages of 2 months and 20 years during 1960, before the usual seasonal rise in poliomyelitis incidence occurred, and this programme is now in full swing. During the first three months of this year about 55 million people (70% of the population under 20 years of age) have received vaccine; of these all have received type 1, 15 million types 1 and 3, and 4 million all three types. In addition, 14 million of those vaccinated in 1959 have been revaccinated with triple vaccine. When the 1960 mass vaccination programme is complete, it is planned to vaccinate all 2- to 12-month-old children routinely.

Sugar Dragées

This vast programme is entirely on a voluntary basis. In each area the work is directed by the local health authorities, who, with the aid of vaccination teams, advise the local doctors responsible for the feeding of the vaccine, store and distribute the vaccine, and direct the propaganda through the press, radio, television, cinema, lectures, and leaflets. The schedule of vaccination most widely used is to feed each type of vaccine separately in the order type 1, 3, and 2, with a 4 to 6 weeks' interval between the feedings, followed by trivalent vaccine 3 to 18 months later. Each dose contains approximately 10^5 tissue-culture infecting doses of virus. The most important factor contributing to the vastness of the programme is the form in which the vaccine is administered. For children up to 8 months of age, liquid vaccine is given in fruit-juice, water, or milk, but for the older children and adults vaccine is fed in the form of sugar dragées. These dragées are prepared by coating spherical pieces of sugar with syrup containing the vaccine and then with an outer sugar-wax layer to prevent drying. The dragées are about 1 cm. in diameter, have an average weight of 1 gramme, and represent one dose of vaccine. They are coloured according to the type of virus they contain—type 1 being pink, type 2 violet, type 3 blue, and those containing all three types white. The vaccine in this form is reasonably stable, retaining its viability for three months at −20° C., for 30 days at 5° C., or for five days at room temperature (25° C.). There is no doubt that the vaccination programmes have been greatly helped by the use of these dragées, and in some towns the daily number of vaccinations has reached more than 400,000.

Safety

The Russians are quite satisfied that the vaccine is entirely safe. Each batch is prepared and tested according to the methods recommended by Dr. Sabin, involving tests to exclude "B," measles L.C.M., E.C.H.O., Coxsackie, and other simian viruses, and to determine the degree of neurovirulence for monkeys. It is considered that the safety of the vaccine was proved during the mass vaccination campaigns in Estonia and Lithuania early in 1959, when the incidence of poliomyelitis in these areas was low and any cases associated with the vaccine would have been easily recognized. It was found that no cases occurred which could be definitely associated with the feeding of vaccine, although it was estimated, from antibody studies, that 750,000 persons susceptible to poliomyelitis had received the vaccine. Further, it was pointed out that in other Soviet Republics there was no evidence of associated cases and no increased incidence in vaccination areas compared with those where no vaccination had been done. Coincidental cases of poliomyelitis have occurred when vaccination has been done in the summer and autumn seasons, but here again it is firmly believed—although little data were presented in support of this—that these cases were not associated. Minor reactions, such as nausea, vomiting, diarrhoea, and general malaise, have been reported after administration of the vaccine, but the number —never more than 3/100,000—is no greater than one would expect in non-vaccinated groups.

Antigenic Activity

Most of the conclusions reached regarding the antigenic activity of the vaccine are based on its ability to produce antibodies rather than on the actual antibody levels attained. In various studies antibody responses were obtained in from 75 to 90% of children originally without antibodies. Serum titres were given in a few cases, and in a study in Estonia mean titres of 52, 162, and 128 were obtained for types 1,

2, and 3 respectively after three feedings. Antibodies may be detected as early as three to four weeks after administration of the vaccine, but how long they last is of course a question to be answered later. Subjects who have poliomyelitis antibodies before vaccination do not respond so well, and, moreover, the response may also be inhibited by interference of the vaccine strains by enteric viruses present in the intestinal tract. This latter effect can be overcome to a certain extent by increasing the number of feedings or by selecting a time for vaccination when interfering viruses are not so prevalent. It should be mentioned that in the case of the Salk vaccine the interference effect of viruses plays no part, and the serological response is considerably enhanced by naturally occurring antibodies. However, the exponents of live poliovirus vaccine point out that this type of vaccine gives a more complete protection, since it produces not only a serological immunity but also a local cell resistance of the intestinal and pharyngeal tissues leading to a reduction in the circulation of virulent epidemic strains of poliovirus in the population.

Virus Excretion

It has also been shown that the vaccine virus is excreted for one to six weeks and sometimes up to four months after feeding, and that where close contact occurs the virus spreads to other susceptible people. This spread of virus from vaccinated to non-vaccinated persons is regarded as a method of obtaining in a closed community a more complete immunization, which finally breaks the process of transmission of virus, thus reducing the possibility of its reversion to virulence. The Russians consider that the same principle applies in the case of mass vaccination carried out over a short period of time in a whole town or region.

Protective Effect

No strictly controlled field trials have been made to investigate the effectiveness of the vaccine in protecting against the disease. Such trials would have been difficult to organize, since the action of the vaccine is not confined only to those persons to whom it is administered. However, much importance is attached to the results obtained in Estonia and Lithuania, where mass vaccination was completed by June, 1959. A striking reduction in the incidence of paralytic poliomyelitis was observed in the later part of the year compared with the earlier part, and also with the corresponding period of the preceding four years. The figures for the seven months, June to December, of the years 1955 to 1959 were as follows:

	1955	1956	1957	1958	1959
Estonia ...	180	213	102	963	8
Lithuania	411	247	124	264	17

Seven of the 8 cases in Estonia and 7 of the 17 in Lithuania occurring in 1959 had received the vaccine, but this was accounted for by the extremely broad coverage of the population by vaccination. Other results pointing to the protective ability of the vaccine were obtained from the Moscow and Karaganda areas, where trivalent vaccine was given in 1959 at the time of the seasonal rise in the incidence of poliomyelitis; the number of cases among the non-vaccinated was approximately 10 times that among the vaccinated. Trivalent vaccine was also considered to be of value when given during an epidemic outbreak in the Tashkent area in 1959; a rapid and striking reduction in the incidence of poliomyelitis resulted, which was attributed to the interference of the vaccine with the epidemic virus.

There is no doubt that the results reported so far regarding the efficacy of the vaccine in protecting against the disease are encouraging, but those obtained during the next few years will be even more interesting, as they should clearly indicate whether the live vaccine is able to bring about the effective control of poliomyelitis.

STUDENT MEDICAL JOURNALS

CONFERENCE OF EDITORS AT B.M.A. HOUSE

[FROM A SPECIAL CORRESPONDENT]

A conference, organized by the British Medical Students' Association with the assistance of the *British Medical Journal*, took place in the Council Chamber, B.M.A. House, on Wednesday, May 25. Mr. J. GUNN, editor of the *British Medical Students' Journal*, took the chair.

The Guest Speakers

After welcoming over 50 delegates from all parts of the British Isles, the chairman introduced Mr. PERCY CUDLIPP, editor of the *New Scientist*, who began by telling the conference the reasons for his journal's existence, the public it expected to reach, and the function it planned to fulfil. He said that there was a need on the part of the teacher and his students, the industrialist and technologist, the specialized scientist, and even the hypothetical "intelligent layman" for a science journal which would neither baffle them with the specialist's jargon nor insult them by "talking down." In spite of early scepticism in Fleet Street, the *New Scientist* planned to obtain the best scientists as its writers and persuade them to interpret their work for the layman: and Mr. Cudlipp felt that this had been achieved. As a non-scientist, he considered his own comprehension a good yardstick: nevertheless, he had found scientists willing to write and all wrote well. He said that he was able to read the whole journal before going to press each week—essential to successful editing in a specialized field. He recalled occasionally reading his own daily paper with great surprise: and, since most of the national newspapers were to some degree political "specialist" journals, he was forced to admit that lack of time to read the whole of any edition considerably increased editorial problems. Saying that he had enjoyed the experience of launching a new journal in the conviction that it would serve a potential readership only recently in existence but growing rapidly, he concluded by stressing the importance of an editor's not only visualizing his reader but also keeping him constantly in mind. Answering delegates' questions, Mr. Cudlipp said that most of his articles were commissioned. But an editor would have either to pay well, or make it felt an honour to be published in his pages, before he might expect to attract contributors of high quality.

The second speaker, Mr. CHARLES MACMILLAN, managing director of E. and S. Livingstone, of Edinburgh, began by agreeing with the first, that the medical publisher also commissions the majority of the works he publishes. Not always, he said, was the pre-eminent specialist most suited to medical authorship: where possible an approach was made to the man known to his students as the best lecturer: such a person was invariably an excellent author as well. It was common knowledge that authorities in medicine disagreed frequently, and never more so than in their opinions of manuscripts. For this reason his own house often relied upon the views of a non-specialist doctor, who might resemble more closely a potential readership. He then went on to describe the more material considerations of a publishing company. He assured the conference that medical publishing was not the path to easy fortune, that many books were not an economic proposition at all, and some were issued simply as a service to a small number of readers. After convincing a delegate from Glasgow that paper-backed editions would not substantially reduce the cost of a textbook, Mr. Macmillan pleaded for fair reviewing in student journals. He said that while publishers were glad to advertise in them and attached importance to the comments of student reviewers, they had a right to expect books not to be dismissed out of hand because of a few minor errors. The discussion ended with lively exchanges on the whole problem of book reviews, in which even

Dr. Clegg, editor of the *B.M.J.*, agreed that he had not enough space for a review of every book received.

Dr. HUGH CLEGG then outlined to the conference the history of the *British Medical Journal*, and of its associated publications. Supporting his observations by quotations of figures and finances, he showed how both the *Journal* itself and the techniques involved in producing it had developed over the last thirty years, accompanied by a steady rise in circulation up to the present figure of 85,000 copies weekly. He said that he had some difficulty in visualizing his reader, for the diversity of the *Journal's* contents made it unlikely that anyone would read the whole of a particular issue. Reading, he said, should be selective. After commenting on many aspects of the *B.M.J.'s* work, from the original papers to the obituary notices, Dr. Clegg advised delegates that brevity, simplicity, and clarity formed the basis of medical writing, as journals had little space to devote to literary extravagance. Delegates' questions were concerned with original papers, and the correspondence and advertisement columns. While the figures concerning the former proved a little depressing, surprise was felt that most of the correspondence received was published.

The morning session ended with an entertaining account of the contributions to the arts made by medical men in the past and present, from Dr. F. N. L. POYNTER, librarian of the Medical Historical Library of the Wellcome Institute. He said that medical knowledge was considered a part of general culture and learning until quite recent years, nor was medical skill confined to doctors alone. The great medical "bibles" were to be found in any learned man's library, and were available to all who could read. In the field of poetry, he felt that, in spite of the many doctors who wrote verse, perhaps John Keats alone merited the description "great." This he ascribed to the difference between the temperament of doctor and poet. Turning to prose and drama, he cited many authors, from Somerset Maugham to James Bridie, in support of the view that doctors were far better suited to these media. Of the painters and musicians, again there were very few distinguished medical ones. Dr. Poynter said he was convinced that every doctor should be acquainted with the arts, believing that general learning was essential to his training and invaluable in his attitude to practice.

Function of a Student Journal

The chairman put forward some of the views which might be held on this theme, relating them to the *British Medical Students' Journal*, before putting the matter to open discussion. At first delegates seemed unwilling to commit themselves to express their own journal's function, until Mr. D. JENKINS, of Queen's University, Belfast, and Mr. G. GELDER, of Sheffield, both said that they were convinced few if any student journals had any function whatsoever. They agreed that, as few articles were contributed voluntarily, they performed no service to authors; and as a small minority of so-called student journals went to students, who read them rarely if ever, little service was performed to the reader either. This view received a measure of support, to which other editors responded with the fact that many were in reality hospital journals, and at least served posterity by recording information not retailed elsewhere. Mr. A. M. STEWARD, of St. Mary's Hospital, said that his journal gave space to the encouragement of many student activities, and he felt that much interest was maintained as a result. This he put forward as a justifying function for his journal. Mr. S. E. MILLER, of Glasgow, suggested that the disillusioned editors had occupied their seats too long. But the reply was that no volunteers could be found. After much discussion on the useful life of a student editor, the chairman put to the conference that in terms of the medical student his journal should provide space in which he might publish if he wished to do so even though it was probable that he would not: and it should seek to publish articles to interest and entertain him, whether he would in fact read them or not. In spite of earlier doubts, this proposition received unanimous support, and the attention of delegates passed to more mundane matters.

Hazards of Business

Mr. D. MASON, an expert on printing matters, introduced a discussion on a survey made of the organization and finances of the journals represented. He urged delegates to seek more information from printers and advertising agents, and to press unashamedly for the best service. He said that there were many obvious anomalies in the returns, and that these could not be put in order unless the business house concerned was obliged to explain them. He summarized the advantages and otherwise of the large and small printing house, and was able to throw much light on varied technical mysteries, from modern methods of illustration-block manufacture to the costing system for galley corrections. Delegates expressed great interest in the survey and report: and it was decided to send copies to every journal.

At the end of the conference, thanks were expressed from the chair to the *British Medical Journal*, for their assistance and hospitality, and to the British Medical Association.

In the evening some 50 to 60 student editors dined at B.M.A. House as guests of the *B.M.J.* Dr. H. A. CLEGG proposed their health, and Mr. JOHN BAKER, assistant editor, *British Medical Students' Journal*, responded.

APPROVED NAMES

The last supplement to the consolidated list of "approved names" was published in the *Journal* of February 6 (p. 417). A new supplement, dated May, 1960, is printed below. Communications relating to "approved names" should be addressed to the secretary, British Pharmacopoeia Commission, General Medical Council, 44, Hallam St., London, W.1.

Approved Name	Other Names	Notes
Amphotericin ..	Polyene antibiotics isolated from a strain of a *Streptomyces* species, referred to as *Streptomyces nodosus* (specific substances are designated by a terminal letter; thus, amphotericin B) "Fungizone" is amphotericin B	Antifungal antibiotic
Benzonatate ..	2-(ω-Methoxypolyethyleneoxy)ethyl *p*-butylaminobenzoate "Tessalon"	Antitussive
Benzthiazide ..	3-Benzylthiomethyl-6-chloro-7-sulphamoylbenzo-1: 2: 4-thiadiazine 1: 1-dioxide "Fovane"	Oral diuretic
Chlormidazole	1-*p*-Chlorobenzyl-2-methylbenzimidazole	Antifungal agent
Chlorzoxazone	5-Chlorobenzoxazolin-2-one	Skeletal muscle relaxant
Cinnarizine ..	1-*trans*-Cinnamyl-4-diphenylmethylpiperazine	Antihistamine
Diethylpropion	α-Diethylaminopropiophenone "Tenuate" is the hydrochloride	Appetite suppressant
Guanethidine ..	1-(2-Guanidinoethyl)azacyclooctane "Ismelin" is the sulphate	Hypotensive agent
Itramin tosylate	2-Nitratoethylamine toluene-*p*-sulphonate "Nilatil"	Vasolidator
Methandienone	17β-Hydroxy-17α-methylandrosta-1: 4-dien-3-one "Dianabol"	Anabolic agent
Methdilazine ..	10-(1-Methyl-3-pyrrolidinylmethyl)-phenothiazine	Antipruritic
Metronidazole	1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole "Flagyl"	Treatment of trichomoniasis
Nealbarbitone	5-Allyl-5-neopentylbarbituric acid "Censedal"; "Nevental"	Sedative
Paromomycin ..	An antibiotic produced by *Streptomyces rimosus forma paromomycinus* D-Glucosaminedeoxystreptamine D-ribosediaminohexose "Humatin" is the sulphate	Treatment of intestinal amoebiasis
Phenethicillin ..	6-(α-Phenoxypropionamido)penicillanic acid; (1-phenoxyethyl)penicillin "Broxil" is the potassium salt	Antibiotic
Pralidoxime iodide	Picolinaldoxime methiodide "Protopam"	Anticholinergic
Sodium ipodate	Sodium β-(3-dimethylaminomethylen-amino-2: 4: 6-triiodophenyl)propionate "Biloptin"	Oral contrast medium
Spironolactone	β-(7α-Acetylthio-17β-hydroxy-3-oxo-androst-4-en-17α-yl)propionic acid lactone "Aldactone"	Control of oedema and ascites
Sulphinpyrazone	1: 2-Diphenyl-4-(2-phenylsulphinylethyl)pyrazolidine-3: 5-dione "Anturan"	Treatment of gout
Thioproperazine	2-Dimethylsulphamoyl-10-[3-(4-methylpiperazin-1-yl)propyl]phenothiazine "Majeptil" is the methanesulphonate	Treatment of chronic schizophrenia

Nova et Vetera

EXETER'S MEDICAL HISTORY

Exeter, with which Torquay is closely linked medically, has much that will interest members of the British Medical Association visiting Torquay for the Annual Meeting. Like other ancient cathedral cities it was in former days an important administrative metropolis. Its association with Drake and Raleigh will be well enough known, but as a medical centre it goes back at least to the twelfth century, when the first hospital was established for much the same reasons as those of St. Bartholomew's and St. Thomas's in London and that of the Holy Cross at Winchester—to care for pilgrims and lepers. This hospital of St. Mary Magdalene later became an almshouse.

Exeter had several other hospital foundations, some for the care of the aged, some for orphans. The latter became schools, one of which, the Blue Maidens Hospital (now developed into the modern Maynard Girls' School), has a special link with Torbay. On November 5, 1688, Prince William of Orange landed at Brixham with 15,000 troops of very assorted nationalities. His first major stopping-place *en route* for London, and the overthrow of James II, was at Exeter, which he entered on November 9. The weather was the worst that Devon can offer, and in wet seasons,

John Haddy James, 1788–1869.

such as the recent winter of 1959–60, it can be really terrible. Prince William's troops suffered much from exposure. At his request the city fathers of Exeter established a temporary hospital at the Blue Maidens. Documents relating to this are still preserved, and in them are given details of the medical condition of soldiers, the drugs used, the provisions, and the names of the surgeons and of the women who looked after the men. William never paid his bill, and in 1706 the citizens appealed to Queen Anne for the sum involved, which amounted to £354 4s. 2½d. History does not relate whether it was ever paid.

The first hospital in the modern sense was completed in 1718: it is the present Exeter City Hospital, and it remained a municipal hospital until 1948, although its original buildings were destroyed by enemy action in 1942. The first voluntary hospital, now known as the Royal Devon and Exeter Hospital, was founded in 1741, and was one of the first great provincial voluntary hospitals established in the eighteenth century. Its original buildings still remain and are in daily use. The board room is well worth a visit, a perfect example of the architecture of the time, with some magnificent portraits of its early worthies: three of them are by Thomas Hudson, the master of Joshua Reynolds, and two by John Opie (that of *John Patch junior: surgeon* is one of the greatest works of this master). Amongst these worthies are also portraits of Dean Alured Clarke, the founder, Thomas Glass, John Lee Dicker, John Patch senior (a portrait which much influenced Reynolds), and John Sheldon, F.R.S., an eccentric genius and one of the pupils of William Hunter, whom he followed as anatomist to the Royal Academy.

Thomas Glass, one of the founders and an early pioneer in vaccination, is also notable in having founded the Exeter Medical Library in 1787: this was greatly augmented by Bartholomew Parr, F.R.S., and by their followers to the present day. Dr. Glass had bequeathed his library to the Cathedral. In 1819 the medical leaders in the city persuaded the Dean and Chapter to allow this collection of books to form the basis of the bigger library established at the Royal Devon and Exeter Hospital, and there they remained until, in 1947, the memory of the Dean and Chapter was refreshed by the approaching nationalization of the hospitals, and, although the library was independent of the Health Service, the Glass collection was reclaimed and is once more housed in the excellent Cathedral Library, which is administered by the University of Exeter but is kept at the Bishop's Palace. The Exeter Medical Library, now in two portions, contains most of the medical classics. It is an outstanding collection and should certainly be visited by those interested in medical history.

During the eighteenth century some sort of medical education was to be found at the Royal Devon and Exeter Hospital, and early in the nineteenth century, influenced by John Sheldon, impetus was given to the formation of a medical school, which continued until 1858. Leaders in this were Samuel Barnes and John Haddy James. Barnes was a leading provincial oculist, and was one of the ancestors of the actress sisters Violet and Irene Vanbrugh. John Haddy James should particularly be remembered at this time, for he was one of those who assisted Charles Hastings in establishing the Provincial Medical and Surgical Association (which was to become the British Medical Association) in 1832. Ten years later he was president of a two-day meeting of the Association in Exeter. His efforts there met with the warm approval of Charles Hastings, as the following letter shows:

Worcester,
August 13, 1842.

Dear Mr. James,

Ever since my return home I have been in a continual whirl of business or I should have earlier written to congratulate you on the singularly successful meeting which we were so fortunate to have under your presidency. I can assure you with perfect truth, that on no occasion do I remember the presidential duties better performed, and every local arrangement was as satisfactory as possible—the Council are about to meet here this evening to make arrangements for the publication of the next Volume of Transactions and I think we shall agree to have a small volume printed as last year.

The question of Medical Reform seems to require no immediate attention but on this I shall probably find it necessary to correspond with you and if anything occurs to you pray write to me.

I am not aware of any subject connected with the association requiring immediate attention but I shall expect to hear from you at any time that you may have suggestions to make to me.

I cannot write further for I am summoned away but you shall hear again.

Believe me yours truly,

CHAS. HASTINGS.

P.S.—I have arranged for a full report of the meeting in the journal.

(The *Journal* had not yet received capital letter status.—N.C.)

(*Continued at foot of next page*)

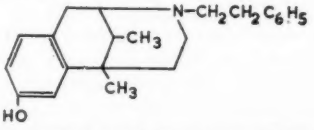
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Phenazocine

" Narphen " (Smith & Nephew).

Chemistry.—Phenazocine is racemic 2′-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan, and has the following structural formula:



Pharmacology.—The analgesic potency of the *laevo*-isomer in mice was about 20 times higher than that of morphine. The *dextro*-isomer was approximately half as active as the *laevo*-rotatory form. Preliminary tests in monkeys indicated a low physical dependence on the drug. Similar results were obtained in man. Clinical trials suggest that 1.5 mg. given intramuscularly at four-hourly intervals controls post-operative pain adequately. Slightly higher doses were successfully used in patients with malignant disease. Phenazocine appears to be about three to five times more effective than morphine in producing analgesia in man.

Therapy.—The therapeutic indications are the same as for morphine. Phenazocine seems to be less liable than morphine to produce respiratory depression and vomiting, but more information on this and on its addictive properties is needed.

Side-effects.—Respiratory depression. Hypotension in 7 out of 160 patients. Constipation.

Contraindications.—The same as for morphine.

N.H.S. Basic Price.—10 1-ml. (2-mg.) ampoules, 18s. 9d.

(*Continued from previous page*)

This year, during the Annual Meeting of the B.M.A. in Torquay, there will be, for those interested, displays of books and documents at both the library at the Royal Devon and Exeter Hospital and at the Cathedral Library, Exeter, where can also be seen the famous Anglo-Saxon *Book of Exeter.*

Further information and references are given in my article "John Sheldon, F.R.S., and the Exeter Medical School" (*Proceedings of the Royal Society of Medicine*, 1959, **52**, 231).

The portrait of John Haddy James is reproduced by kind permission of the Governors of the Royal Devon and Exeter Hospital.

NORMAN CAPENER.

JENNER THE MAN

There have been several lives of Jenner—from Dr. Baron's full and somewhat ponderous biography of 1827 to the excellent and authoritative work, *A Bio-bibliography of Edward Jenner*, by W. R. LeFanu, published in 1951.

Dorothy Fisk's biography presents Jenner from a different aspect.* She has assembled all the facts of Jenner's life with care and accuracy. She describes his upbringing, his coming to London as John Hunter's pupil, his return to Berkeley to practise, his study of the cuckoo, his introduction of vaccination, and his triumphs and disappointments resulting from this achievement. Her main purpose is to show us Jenner the man—the humane physician, the poet, the naturalist, the good husband and father, and the friend. The result is a delightful book which doctors will enjoy and can recommend to their patients and friends. One or two slips should be corrected in the next edition. On p. 109, for example, fleas are implicated as the vectors of Jenner's typhus instead of lice.

ARTHUR S. MACNALTY.

**Dr. Jenner of Berkeley.* By Dorothy Fisk. (Pp. 288+vii; illustrated. 25s.) London, Melbourne, Toronto: Heinemann. 1959.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Allergy to Tetanus Antitoxin

SIR,—The article by Dr. I. B. Sneddon (May 14, p. 1468), describing a severe and prolonged allergic reaction after a test dose of 0.2 ml. of a 1 in 10 dilution of tetanus antitoxin, raises several points of interest. While an induced sensitization to an injection of tetanus antitoxin is not uncommon (horse-serum sensitivity is seen in the eczema, asthma, hay-fever group of patients), this seems to be the first recorded case of sensitivity developing to the very small amounts of tetanus antitoxin that normally would become airborne when giving an injection.

Sensitivity to streptomycin in nurses who give injections of streptomycin is a well-known hazard, and special recommendations have been promulgated to diminish such sensitization arising. Nurses who become very sensitive may reach the stage when merely going into a ward where streptomycin is given will start off irritation of the eyelids. The antigenic dose involved in these acutely sensitive personnel must be infinitesimal. If a test dose is given to such a patient, 1 µg. may be a gross overdose. In other words, a test dose on a nurse with suspected sensitivity must be at least 100,000 times less than the patient-dose. On the other hand, a patient receiving 1 gramme streptomycin daily who becomes sensitized to the drug can safely be test-dosed with a dilution of 1 in 10.

It is very easy to be wise after the event, but Dr. Sneddon states " despite the absence of an allergic history." Surely the history clearly indicated that it was likely that his patient was allergic and allergic to a very high degree? A test dose of 0.2 ml. of a 1 in 10 dilution was likely from the patient's history to cause a severe reaction. Such a test dose in a known horse-sensitive patient has been known to cause death. I would therefore make the plea that the much simpler and safer procedure of using a prick test dose (this can also be called a skin test) of the undiluted antitoxin first be carried out if sensitivity is suspected. This introduces about five millionths of an ml. which is one thousand times less than the dose used by Dr. Sneddon. Even this dose very occasionally will cause a mild general allergic reaction.

Dr. Sneddon states that tetanus toxoid does not contain anything likely to cause sensitization. I agree that tetanus toxoid is the least likely of all prophylactic injections to cause allergic trouble. However, it has caused death, and I believe that with the new synthetic casein medium that is used to grow the tetanus bacillus sensitization to this vaccine is on the increase, especially if looked for. It is as well to remember that any injection may contain known or unknown allergens. Moreover, any injection which gives rise to protective antibodies may also sensitize and give rise to allergic antibodies.—I am, etc.,

A. W. FRANKLAND.

Allergy Department,
Wright-Fleming Institute of Microbiology,
St. Mary's Hospital, London, W.2.

Recruitment and Training of Nurses

SIR,—Your annotation entitled " Selection and Training of Student Nurses " (April 9, p. 1120) mentions the *Report of Nursing Committee* published by the Northern Ireland Hospitals Authority, 1960. This report makes clear the valid distinction between basic nursing and technical nursing, and to recruit more nurses for the basic care of patients it recommends the expansion of the facilities for training of State-enrolled assistant

nurses and curtailment of facilities for training for State registration.

Dr. I. M. Librach (May 7, p. 1429) does not recognize this distinction and wants all nurses to be trained to the same high standard, and extra help on the wards to be given by ward orderlies, porters, domestics, or nursing auxiliaries—presumably untrained. The basis for the distinction between the two grades of nursing is the fact that many nursing procedures can be correctly performed by nurses who have not had the long theoretical training necessary for the present State registration. But these are nursing procedures and should be carried out by nurses, not orderlies, etc.

It does not follow that the existing grade of assistant nurse is correct. I have no recent experience of working with State-enrolled assistant nurses and can say nothing about their training capabilities or usefulness, but the name "assistant nurse" is surely wrong. Another undesirable feature is that this grade is a dead-end from which there is no advancement except by starting again at the bottom of another ladder as a student nurse. Can we imagine any girl of school-leaving age wanting to become and remain an "assistant nurse"? A few days ago two student nurses in the hospital to which I am attached failed to pass out of the preliminary training school. Matron advised them to train for the assistant nurses' roll. Both had the potentialities of excellent practical nurses, but neither would consider becoming an assistant nurse.

The whole structure of the nursing profession should be reorganized to abolish the unfortunately named grade of assistant nurse and replace it by a grade which would be the first stage on the way to the equivalent of the present State registration. Almost invariably the first job a State-registered nurse obtains is staff nurse in a hospital. Why not recognize that fact? The present State-registered nurse could easily be renamed State-registered staff nurse—S.R.S.N.—allowing the lower grade to be State-registered nurses.

The training for the new State registration would be essentially practical and last about 18 months, and the registered nurse would be expected to be competent in all bedside nursing and the administration of medicines and injections and in minor dressing procedures. She would not be expected to know any theory nor would she be expected to be in sole charge of a ward with the responsibility for drugs—dangerous or otherwise. Training for this grade should be in all those hospitals which are at present recognized training schools for registered nurses or assistant nurses, but the qualifications required by the tutors could be much lower than those demanded now in nurse-training schools. Those State-registered nurses of sufficient educational attainment could proceed to selected hospitals for training for the higher qualification of S.R.S.N. Fully qualified tutors, of which there is a shortage, would probably be confined to those training schools.

The small hospitals which are now in danger of losing recognition as nurse-training schools are much more likely to co-operate in a scheme as outlined above rather than lose status and become training centres for State-enrolled assistant nurses. The proposed scheme would also bring the nursing profession into line with the medical profession with a single register, and the registration of higher qualification in general nursing, midwifery, mental nursing, etc., as they are obtained.—I am, etc.,

Banbridge, Co. Down. H. W. GALLAGHER.

"Imferon" and Cancer

SIR,—I have read with interest Dr. J. G. A. Pedersen's letter (May 21, p. 1564) on the carcinogenic action of imferon. There may, however, have been some misunderstanding between us. Certainly we[1] were of opinion that the carcinogenic effect is decided mainly by the absolute amount administered, and only secondarily, if at all, by the relation of this to the body-weight. We saw no evidence to suggest that over-saturation of the organism with iron is a necessary factor in the induction of sarcomata at the injection site, although it was doubtless responsible for the observed yield of tumours in distant organs. Since repeated subcutaneous doses of 0.2–0.3 ml. of imferon produce a high yield of sarcomata in the mouse, we could not feel confident that total doses of (say) 60 ml. intramuscularly in man would necessarily be harmless.

Since the date when our paper was published, this feeling has been strengthened by the observation of sarcomata in mice following repeated weekly subcutaneous injections of imferon of 0.05 ml., in an experiment which still continues. I agree we have insufficient data to allow precise comparison of the carcinogenicity of imferon with that of certain other absorbable iron compounds, and it well may be, as Dr. Pedersen concludes, that great caution must be recommended regarding the dose of iron injected subcutaneously or intramuscularly, or possibly even intravenously, in man.—I am, etc.,

Institute of Cancer Research, London, S.W.3. ALEXANDER HADDOW.

REFERENCE

[1] Haddow, A., and Horning, E. S., *J. nat. Cancer Instn*, 1960, **24**, 109.

SIR,—In their report (May 7, p. 1411) describing the coincidence of a metastatic tumour at the site of injection of iron-dextran complex ("imferon") Drs. J. D. Crowley and W. J. S. Still draw attention to the residual iron and state that the large number of iron-containing histiocytes "was greater than that reported at similar injection sites by Golberg (1960)." We consider that the unique features of their case lie not in an unusual amount of residual iron but in the development of an exuberant fibrous reaction in the subcutaneous fat, and in the presence of "intense reactive hyperplasia induced in the subcutaneous tissues by the injection of iron dextran." It is not clear whether the authors regard these features as normal accompaniments of iron-dextran injections in human tissues. In fact they are grossly abnormal and must be considered as peculiar to the particular case described.

Our own human material shows that the only abnormal finding in the skin and subcutaneous tissues some weeks after an injection of iron-dextran complex is the presence of iron-laden macrophages. Fig. 1 illustrates skin taken 23 days after a *subcutaneous* injection of 2 ml. of imferon. At this time all the iron visible histochemically is intracellular. Though we have not had an opportunity of examining human tissues from areas of "imferon staining" at five to six months following imferon injection, as Drs. Crowley and Still have done, we see no alteration in the histological picture in material taken at one, two, or more years following a course of injections (Fig. 2). In none of our material have we ever seen evidence of fibrous reaction or reactive hyperplasia.

The small amount of iron illustrated in our Figs. 1 and 2 and in Fig. 2 of Drs. Crowley and Still contrasts markedly with that found in experimental animals treated according to Haddow and Horning.[1] Fig. 3 shows a small area of the subcutaneous injection site after only 10 weekly injections of 0.2 ml. iron-dextran into a mouse. Even this is less than the doses used to induce sarcomata in these animals. The whole of the subcutaneous tissue in the injection site is packed with iron-laden macrophages obliterating the original structures. In some places transitions from the macrophages to fibrous tissue can be

clearly seen. The underlying muscle in these animals undergoes a continuous process of necrosis and regeneration in the neighbourhood of iron deposits. In our opinion there is little in common between the human cases and these grossly overloaded animals.

Finally it is worth pointing out that the tissues examined by Drs. Crowley and Still were from the neighbourhood of a necrotic tumour and had been subjected to operative trauma and irradiation, factors which in our experience are more liable than the haemosiderin within the macrophages to produce the reactions described. We feel, therefore, that there is really no evidence to support the conclusion that the "intense reactive hyperplasia" was induced in the subcutaneous tissues by iron-dextran.

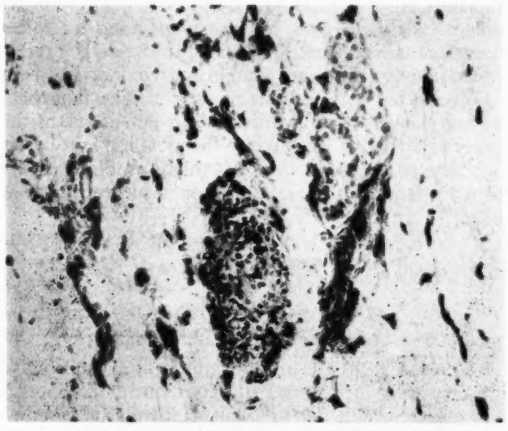


FIG. 1.—Subcutaneous iron-laden macrophages showing tendency to aggregate around sweat glands; 23 days after subcutaneous injection of imferon. (Perls's iron. ×170.)

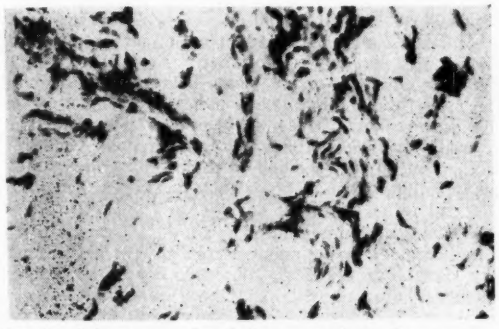


FIG. 2.—Subcutaneous iron-laden macrophages from an area of skin staining two years after a therapeutic course of imferon. (Perls's iron. ×170.)

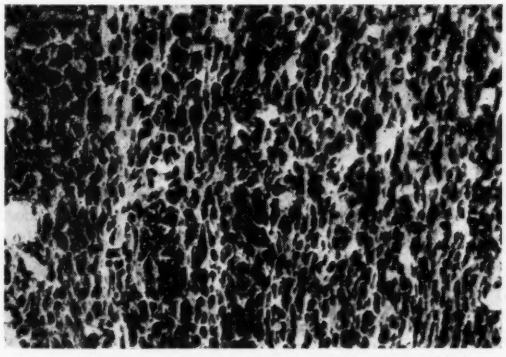


FIG. 3.—Site of 10 weekly subcutaneous injections of imferon in the mouse, showing typical accumulation of iron-laden macrophages. (Perls's iron. ×170.)

Our thanks are due to Mr. Lynn A. J. Evans, F.R.C.S., who provided the skin for the section shown in Fig. 2.

—We are, etc.,

Research Department, Benger Laboratories Ltd., Holmes Chapel, Cheshire. L. GOLBERG.

Department of Pathology, Christie Hospital and Holt Radium Institute, Manchester. J. P. SMITH.

Department of Pathology, University of Manchester. S. B. DE C. BAKER.

REFERENCE

1 Haddow, A., and Horning, E. S., *J. nat. Cancer Instn*, 1960, **24**, 109.

Urogenital Infection and Arthritis

SIR,—"It is a problem the importance of which cannot be overestimated, for its solution might well open the way to a proper understanding of a widespread communicable disease, a serious eye disease, and perhaps the rheumatic diseases as a whole." This, the concluding sentence of your leading article on ankylosing spondylitis and urogenital infection (March 19, p. 865), needs but the addition of psoriasis/keratodermia blennorrhagica to become a complete restatement of the views urged by me with but little success in your correspondence columns[1] for the past ten years. As the full value of this view to future research depends upon an accurate appreciation of present knowledge, I would like to make the following points.

Chronic Prostatitis.—The diagnosis of this condition rests purely on empirical criteria of the microscopical appearances of mechanically expressed prostatic fluid, and let it be added that increasing the number of empirical counts in no way increases accuracy. Furthermore, the fact that some 20 to 40% of normal controls show similar findings gives added point to the point that any conclusions based on investigation into "chronic prostatitis" are utterly useless in our present state of knowledge.

Serological Tests for Rheumatoid Arthritis.—It cannot be too often stated that there are no such tests; all that may be said is that there are cases of arthritis in which certain tests are positive, but, since we are ignorant of why they are positive, it is presumptuous and inaccurate to state that these cases constitute a disease *sui generis*.

Urethritis.—Much confusion still exists on this subject, due, I believe, to the fact that non-gonococcal, non-specific, and abacterial are often used as interchangeable terms, and in the following short résumé I will attempt to clarify the field and introduce new knowledge uncovered over the past 20 years which has as yet been imperfectly assimilated.

For all practical purposes there are four types of urethritis: (1) gonococcal urethritis, (2) *Trichomonas vaginalis* urethritis, (3) urethritis giving an abacterial smear which *sometimes* accompanies abacterial pyuria (primarily a bladder condition), and (4) non-specific urethritis (A and B). Since a known organism is present in (1) and (2), difficulty in diagnosis can only arise between (3) and (4). However, if it is remembered that (3) occurs in the course of a primarily bladder condition it must be associated with signs of cystitis—i.e., frequency, with haze in both glasses in the simple two-glass test. The abacterial smear obtained from this type of urethritis cannot therefore fail to be correctly interpreted, and the diagnosis is confirmed by the complete cure following injections of N.A.B.—a method of treatment useless in type (4) below.

In the light of modern knowledge it can be stated that the three types of urethritis described above are never responsible for complications in joints, eyes, and skin, and any lingering doubts to the contrary must be discarded. Type 4—non-specific urethritis (A and B)—has all the hallmarks of a specific disease, and diagnosis presents little difficulty if attention is paid to its distinctive clinical features, combined with simple laboratory tests. It will be noted, however, that I use "non-specific urethritis (A and B)" to describe this condition. I do this deliberately to emphasize that this type of urethritis may arise from: (1) externally by way of sexual contact with a partner in whom no specific lesion can be demonstrated; and (2) endogenously following various bowel disorders. In every other respect, however, the urethritis is identical, and, furthermore, it is the only type of urethritis, whether arising exogenously or endogenously, that is complicated by joint, eye, and skin lesions in all and every combination.

Thus it will be seen that Reiter's disease, whether fully developed or in *formes frustes*, is but a synonym for non-specific urethritis and its complications. Research into the cause of this type of urethritis, although singularly unsuccessful to date, should for this very reason stimulate us to further efforts, since the difficulty in identification merely duplicates what one would be led to suspect from our failure over many years to find an organismal cause in rheumatoid arthritis, and so may I once more repeat my pleas: "Let us find the cause of non-specific urethritis, as defined above, and thus provide the key to the problem not only of rheumatoid arthritis but of psoriasis and many serious eye disorders."—I am, etc.,

London, S.E.5. F. L. LYDON.

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Eradication of Malaria

SIR,—I was surprised that in the leading article entitled "Eradication of Malaria" (April 2, p. 1033) there was no mention of drugs. The undue emphasis on insecticides indicates a one-sided and even prejudiced point of view. To say that there are "not even any plans for the eradication of malaria in the greater part of Equatorial Africa" is nonsense and shows that your reviewer is out of touch with events. Before making sweeping and derogatory remarks it is advisable to have some knowledge of the facts.

Recently we have been attacking communal malaria with drugs, and results have been so encouraging that we feel this method should be tried on a large scale. If this is not a constructive plan for the eradication of malaria in Equatorial Africa I do not know what is. The method has the advantage of being much cheaper than the insecticidal approach, which in Equatorial Africa has proved inefficient anyway.

We have administered "daraclor" (pyrimethamine and chloroquine sulphate) at fortnightly intervals to 1,200 Africans in a small native settlement near Mombasa where malaria is holoendemic; the parasite rate varied from 70 to 80% and the sporozoite rate was 10%. *Anopheles gambiae* and *A. funestus* are the vectors, both species being prevalent throughout the year. The parasite rate dropped from 70% to zero in less than three months, but the sporozoite rate fell more slowly and is still 4%. It is known that *A. gambiae* can live 86 days in the laboratory, and probably lives much longer in nature. Perhaps some of the *A. gambiae* still positive were infected before the drug was first administered. Another possibility is that infected mosquitoes are coming in from adjacent villages. It rather looks as though in holoendemic areas the sporozoite rate is a more sensitive index of transmission than the parasite rate. Obviously transmission will continue as long as sporozoites are present in mosquitoes. We intend to enlarge the scope of the experiment and to administer drugs to natives in adjacent villages, as well as in the settlement area. It will be interesting to see whether sporozoites will disappear.

In Equatorial Africa there have been insecticidal campaigns in certain areas; these have failed to stop transmission. Should not antimalarial drugs be tried out in a similar way? If not, why not? After all, Pinotti obtained striking results in Brazil by adding chloroquine to the salt. Should not your reviewer have mentioned the work of this pioneer? The fact that he did not shows a certain resistance to new ideas. I think I have said enough to convince the most hardened sceptic that here is a basic policy that might eradicate malaria from Equatorial Africa. Whether it succeeds time will show.—I am, etc.,

Division of Insect-borne Diseases, Medical Research Laboratory, Nairobi, Kenya. R. B. HEISCH.

Urinary Test for Imipramine

SIR,—The wide use of "tofranil" (imipramine) as an anti-depressive agent and the consequent likelihood of overdosage, accidental or otherwise, calls for a reliable method of detecting the presence of this substance in the urine. The following is a description of a simple clinical method which was devised at this hospital and has been successfully used here for some time.

Method.—2 ml. of urine and 1 ml. of concentrated hydrochloric acid are mixed together. A small quantity of potassium chromate or potassium dichromate is then added. The presence of imipramine is indicated by the appearance of a green colour. A few drops of 50% chromate solution is usually sufficient to produce the colour change, but another satisfactory method is to add a "knife point" of the crystalline form. This is then quickly shaken into the acid and urine mixture.

Results.—At imipramine dosages of 150 mg. daily and above, colour changes ranging from an emerald green to a very dark blue-green are obtained, depending upon the amount of drug present. At lower concentrations of the drug—e.g., 75 mg. daily—the colour tends to be somewhat muddy and indistinct, and sometimes gives a negative result. Since the colour tends to fade rapidly, readings should be carried out within 30 seconds of mixing. No false-positives have been found to date. Normal urines turn to a deep amber or reddish tint. Other commonly used drugs—e.g., phenothiazines, P.A.S., and salicylates—usually give a red or port-wine colour change depending upon their concentration. Barbiturates likewise give a negative response.

Concentrated sulphuric acid may be used as an alternative to hydrochloric acid, 0.25 ml. being added to the original amount of urine and chromate. Here, however, the *p*H is critical. If more or less acid is added, the result is less reliable. Again, the colour changes obtained by this method tend to be very impermanent, fading within a few seconds.

I wish to thank Dr. R. Gordon McLaren, Medical Superintendent, and the medical and nursing staff of Oakwood Hospital for their co-operation in enabling this work to be carried out.

—I am, etc.,

Oakwood Hospital, Maidstone. J. G. HEGARTY.

Stripping Varicose Veins

SIR,—I would like to call attention to a complication which occurs in the stripping of varices. I refer to the shredding of the main trunk which very occasionally happens. This leaves the vein, often in its full length, split wide open.

This complication is rare provided the head of the stripper is large enough and the main branches joining the trunk are resected prior to pulling the stripper through. In spite of these precautions we are sometimes faced with a shredded internal saphenous vein which we used to extract with a Mayo ring stripper.

I have recently, however, evolved a much less traumatic method, and that is to pass the stripper wire down the *track* of the torn vein from groin to ankle. It will be found that by tying the stripper head to the shredder vein in the groin the remnants can be extracted quite easily.—I am, etc.,

London, W.1. R. ROWDEN FOOTE.

Uterine Haemorrhage due to Abnormal Vessels

SIR,—The article by Dr. R. Salm and Mr. P. N. Simons (May 21, p. 1534) will serve as a timely reminder that uterine pathology may remain undiagnosed until the organ has been removed from the body. The performance of hysterectomy for menorrhagia in the absence of an adequate diagnosis is a course that most gynaecologists will be forced reluctantly to adopt from time to time, and it is always gratifying when a pathological lesion can be demonstrated in the specimen. The presence of some abnormality in the blood-vessels of the myometrium might be suspected when bleeding is exceptionally profuse but of short duration, and especially when it fails to respond to norethynodrel. A recent case is described below.

A married woman, aged 29, presented with catastrophic haemorrhage for which her practitioner had asked for the "Flying Squad" to be summoned, as he did not think she would survive the short journey to hospital. She had three children aged 8, 3, and 8 months, with a history of hydatidiform mole six years' ago. Episodes of menorrhagia of variable severity had commenced after the second confinement, but investigation had been suspended during her third pregnancy. Severe bleeding had recurred after removal of a thyroid adenoma when the baby was 5 months' old.

Examination showed her to be severely exsanguinated with a pulse rate of 150 and a soft uterus. The possibility of abortion was denied. In hospital she received a massive transfusion and no blood dyscrasia could be found. "Enavid" (norethynodrel) orally controlled her bleeding, but it recurred the following day and another blood transfusion was given. The uterus was then explored, but this was impeded by the profuse flow of arterial blood that emerged through the hollow dilators, exactly as though the bladder were being catheterized. The endometrium was secretory and showed no significant abnormality. Although tight packing of the uterine cavity had controlled the blood flow, laparotomy was advised with a provisional diagnosis of invasive hydatidiform mole, even though there had been two intervening pregnancies. The uterus appeared subinvoluted, but with one area of extreme vascularity where blood seemed to be oozing through the peritoneal surface. Hysterectomy was performed, and Dr. C. W. Taylor reported that this area was honeycombed with abnormal thick-walled blood-vessels passing through the wall of the uterus from peritoneum to cavity.

There was no sign of hydatidiform mole or of trauma, and the appearances were not those of haemangioma. It was concluded that it represented subinvolution of uterine vessels that had supplied the placental site of the second pregnancy.—I am, etc.,

Birmingham. WILFRID MILLS.

Natural Childbirth

SIR,—Your annotation entitled "Natural Childbirth" (March 12, p. 790) mentions a study in that field by R. N. Chamberlain, the Read methods, their employment in British and American centres, including Yale, the Russian "psychoprophylactic method," and also the books of P. Vellay and of L. Chertok, of France. You report that Dr. Chamberlain maintains that, while the Read method differs from the Russian in rationale, they share common ground and that "both blend with the technique of light hypnosis."

Dr. Read ascribed[1 2] his method to reading my books *Progressive Relaxation* and *You Must Relax*, and I have discussed the Read method.[3] I have tried to bring out clearly[3 4] the character of relaxation methodology if applied according to controlled methods of physiology and of physiological psychology. I have emphasized that doctors cannot know whether the patient is really relaxing or not unless action-potential measurements are employed to control the procedures. Unfortunately, electroneuromyometry is highly technical, since it is based upon the use of apparatus accurate to a minor fraction of a microvolt. Adding to the technicalities is the fact that progressive relaxation methodology requires prolonged instruction, which cannot be had from books alone, any more than can chemistry or engineering.

Dr. Read stated that he failed to accomplish his aims until he learned of my methods from my books. However, he received no personal instruction here. Accordingly, when he has been accused of introducing an element of therapeutic suggestion into his methods without knowing it, I have not been in a position to debate the matter. However, therapeutic suggestion has been studied carefully in this clinic and has been discarded. Training courses here are designed to omit it carefully. The patient influenced largely through hypnotic or other therapeutic suggestive means, we find, does not learn technical skills to relax under conditions of discomfort or pain, and he fails to face the reality of the hardship. Practitioners of hypnosis commonly assume that they really produce neuromuscular relaxation when they command their subjects to "relax." As scientists, we can agree with them only if this is demonstrated objectively. We hold ourselves to the same objective standards.

Dr. F. Syrowatka, of Moscow, evidently does not agree that the Russian methods toward painless labour depend on hypnotic suggestion, for he is quoted[5] as saying that many (Russian) obstetricians have tried hypnotic suggestion, but this method has not been widely used because in deep hypnotic sleep the patient cannot actively co-operate during delivery, and cannot give signs of alarm in case of a complicated delivery. In *Progressive Relaxation*[4] I specified thirty-three points of difference between hypnotic methods from those of physiological relaxation. Recently I have added others. Experimental psychologists have agreed. In my experience with hypnosis, which dates back to 1909, I have found no marked difficulty in distinguishing the two fields. One important difference is the autonomy cultivated in and through relaxation physiology. Whatever usefulness of hypnosis for investigative purposes, like the British neurologists of the first world war, we find that it accomplishes little or nothing that cannot be duplicated or bettered by other methods. Furthermore, like Emil Kraepelin, we find the use of hypnosis generally unwarranted. In my experience it tends to undermine the sense of reality in patients and to render them more rather than less neurotic. It diminishes the very autonomy which is the chief aim and purpose of differential neuromuscular relaxation methods.

In recent articles Professor E. Gelhorn[6 7] has performed certain crucial experiments on laboratory animals to test my findings on human subjects. With electrodes implanted in the region of the hypothalamus and also in cortical centres, he confirms my findings on human subjects that with advancing neuromuscular relaxation emotional and cortical activities subside. In view of our results, it would seem fitting that students first pursue the necessary steps to become really familiar with methods of physiological relaxation. They might ask themselves, "If neuromuscular relaxation is identical with hypnosis, what is neuromuscular tension?" Both tension and relaxation are regarded by physiologists as fundamental vital processes. Possibly the future of scientific medicine may be favourably influenced by an adequate rather than a superficial understanding of the nature of relaxed states in contrast with tension states and disorders. Neglect of physiology can never accrue to the advantage of medical practitioners.—I am, etc.,

Laboratory for Clinical Physiology, Chicago, U.S.A. EDMUND JACOBSON.

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Treatment of Simple Hirsutism

SIR,—I was pleased to note that my experiences with cortisone in the treatment of constitutional hirsuties have been much the same as those reported by Dr. D. Mattingly, Dr. I. H. Mills, and Professor F. T. G. Prunty in their interesting and important article (April 30, p. 1298). An occasional case has responded well, but the response in the rest has been undramatic. They did report, however, that growth slowed slightly, and the hair became finer and lighter. Wishful thinking cannot be wholly excluded, but the reports were so uniform that there did appear to be some grounds for acceptance. Dr. I. H. Gordon and I weighed the amount of hair grown on a marked square for a month in six patients before and after the use of cortisone. No difference was observed in five, but a quite marked change was remarked in the sixth.—I am, etc.,

North Middlesex Hospital, London, N.W.8. D. G. FERRIMAN.

Spiritual Healing in Hospitals

SIR,—May I, as a practising doctor, make my protest and my regrets that certain hospital committees have so little confidence in their medical and surgical staffs that they have seen fit to return to the cave by encouraging the belief in the control of man's environment by magical means? I refer, of course, to so-called spiritual healing through the agency of the laying on of hands.

It is not easy to understand how their decision was made. It may be that such therapeutic practice would only be recoursed to if the patient requested it. If this be so, then it is a clear case of the patient dictating his own treatment, a condition which I could not imagine happening in any properly run hospital, the legal responsibility meanwhile resting on the shoulders of the unfortunate doctor in charge. The great advances in medicine were not made by pious supplicants but by acute observation and rational thinking. This outrage is a betrayal of these principles and should be strenuously resisted.

Quite apart from these questions, the hospital authorities concerned may well be transgressing the law governing covering in allowing untrained and unqualified people to take part in treatment.—I am, etc.,

Glasgow, W.2. VERNON R. NURSE.

SIR,—I read your leading article (May 7, p. 1417) on the subject of spiritual healing with great interest and should be most grateful for the hospitality of your columns to set out some points concerning admission of members of the National Federation of Spiritual Healers to work in the hospitals, points which carry weight with some of us who, with many years' practice behind us, have come to regard such problems from a philosophical angle as well as scientific.

Throughout history a few people of various religions have been credited with the possession of the "Gift of Healing." It is mentioned by St. Paul in 1 Corinthians, xii. A tradition lasting through thousands of years is likely to be based on fact. Secondly, before we condemn the efforts of the healer as valueless we should scrutinize our yardstick. He may not bring down a dangerously high blood pressure (though I have known that done), but he might aid the patient to gain a peaceful mind and relaxed body, which would be of great comfort to him and to his relations, as well as aiding all other forms of therapy. With time to get to understand the patient's family background, he could fill part of the role of the family doctor at the beginning of the century, of whom it was so often said, "I always feel better after he has been." In this scientific age we are in danger of losing sight of these valuable imponderables. Have not recent researches put extra-sensory perception on the scientific map? Medicine should involve a marriage of Science and Art. Outside our profession some very deep thinkers, such as D. H. Lawrence, have voiced the fear that we may get so scientific that we are blind to all except body and reduce a human being "to the level of a thing."

Lastly, a considerable proportion of those hospital patients who will seek the ministrations of the healer will do so because they know that their days are numbered. The healer's visit then has special value in giving assurance that no stone has been left unturned. I hold that any sensible person who has the will to help is a potential healer.—I am, etc.,

Farnham, Surrey. CYRIL V. PINK.

SIR,—The management committee of this hospital is one which has given Mr. Harry Edwards and his colleagues permission to visit patients, and I support their decision. The medical interest of the patient is safeguarded because these spiritual healers may only be admitted if the consultant in charge of the case is satisfied that in his opinion no harm is likely to be done.

It is my view that a patient has the right to request and receive treatment in the form of spiritual healing from any source, whether from clergy of orthodox Christian denominations or from lay faith healers. This request can be refused by the consultant in charge if it is clearly dangerous, and the patient can, if he insists,

leave hospital. The medical profession has not got a monopoly of success in curing disease. Witchcraft in Africa, faith healers, naturopaths, spiritualists, laying on of hands, visits to Lourdes, etc., do sometimes cure where we fail. I am sure that their success is due to scientific laws about which as yet we know nothing.

All spiritual methods of healing, however wrong the theories used to explain these effects, are forms of psychotherapy. I have no doubt that successful results are primarily due to the positive transference between patient and healer together with an explanation that has meaning for the patient. We have no right to refuse a chance of cure from any source when we have failed. We have every right and a duty to warn our patients of the danger inherent in some of these unorthodox practices, but we have no right to deny our patients access to them if they so wish.

Finally, it is highly dangerous to allow the State to dictate to doctors who shall or shall not be admitted to our hospitals. This is totalitarianism. The doctor alone must decide what is best for his patient—not the State—and the patient alone must decide after being given full knowledge of his case whether he wishes to abide by his doctor's advice. Furthermore, it is our duty even when our patients decide on a foolish course of action to be ever willing to accept their decision without moralizing and to continue our administrations even if the meddling of spiritual healers makes them worse and to rejoice with the patient if unorthodox methods produce a cure. I have no doubt whatsoever that unorthodox practitioners and the ministrations of orthodox Christian priests and ministers bring relief and comfort to thousands of patients suffering from psychosomatic disorders where we as yet fail. We have no right to refuse our patients access to their ministrations. We can do this without violating the G.M.C. rule forbidding co-operation with unregistered practitioners. —I am, etc.,

The Towers Hospital, Humberstone, Leicester. H. B. KIDD.

SIR,—I trust that, because I live in the Antipodes, I am not too late to enter the lists on the side of your Deva Hospital correspondents (March 26, p. 962) on this highly important subject. Its importance rests on two considerations which lie at the very root of medical practice. The first is historical: all that the Fathers of Medicine have achieved in the face of desperate odds by their insistence on the scientific method of observation and mensuration is in jeopardy, should we allow ourselves to slip back to the hocus-pocus of mediaeval concepts. Your correspondents (e.g., Mr. Griffith Evans, April 9, p. 1134) have used words such as "soul" and "spirit" as though they had an exact meaning. Expressions such as "the laying on of hands" must have puzzled thousands of your readers because, not being Christians, they do not know this to be a quotation from King James's English translation of the Bible.

The second is disciplinary: the General Medical Council forbids us to associate with unqualified persons, and surely we all whole-heartedly endorse and obey this rule. No doubt it is within the competence of the Minister of Health to allow whom he chooses to treat his hospital patients, but he cannot and shall not direct both us and unqualified persons to treat the same patient. It is imperative that the B.M.A. refers this matter to the G.M.C., but I have no doubt that that council's verdict will be the same as it has been in the case of others such as osteopaths, chiropractitioners, and so forth, even though these are very often skilled healers—to wit, let them qualify first in accordance with the Medical Acts. In the case of members of the National Federation of Spiritual Healers the G.M.C. would not be unreasonable if it insisted on their obtaining the D.P.M. before they practise faith-healing in collaboration with us.—I am, etc.,

Mansfield, Victoria, Australia. L. EDWIN VINE.

*** In the Notice issued by the Disciplinary Committee of the G.M.C. for the guidance of general practitioners, the paragraph (5 (d)) on "covering" and on relations with persons performing functions relevant to medicine includes the following: "(1) Any medical practitioner who by his presence, advice, or co-operation (whether by the administration of anaesthetics or the issue of certificates or otherwise) knowingly enables or assists a person not registered as a medical practitioner to practise medicine, or to attend or perform any operation on a patient in respect of any matter requiring medical or surgical discretion or skill, is liable to erasure. . . . (3) Nothing in the foregoing paragraphs is to be regarded as affecting or restricting in any way (i) the proper training of medical and other bona-fide students, or (ii) the legitimate employment of nurses, midwives, physiotherapists, dispensers, and other persons trained to perform specialized functions relevant to Medicine, Surgery, and Midwifery, provided that the medical practitioner concerned exercises effective supervision over any person so employed and retains personal responsibility for the treatment of the patient."—ED., *B.M.J.*

First-aid in Aircraft

SIR,—Some years back one of my teachers, Mr. Wilson Hey, of this city, pioneered a movement for the administration of morphine to severely injured persons in mountaineering accidents. I now wish to emphasize as strongly as I can that the same facilities should be applied to aircraft, to be administered only by direction of the commander of the aircraft.

I have recently finished a tour of the Near East by plane, and during a flight across the desert one passenger sustained a fractured nose and several others were ill with air sickness. Another passenger, who fortunately kept well, was an old lady of 81 years, but who could quite easily have sustained a fractured femur on her way to and from the toilet whilst the plane was rocking. Inquiry from the stewardess revealed the striking fact that the only analgesic aboard was a supply of A.P.C. tablets, and the first-aid kit in general was on the scanty side.

I feel, Sir, that the time is now ripe for a general review of the whole situation of medical aid to aircraft passengers.—I am, etc.,

Manchester, 19. F. REYNOLDS.

Petrol-vapour Poisoning

SIR,—Dr. R. W. Ainsworth in his description of a fatal case of petrol-vapour poisoning (May 21, p. 1547) mentions "interesting skin changes, probably due to the contact of petrol-soaked clothing after death."

In 1949 I made a journey by air from Abadan. This lasted about 70 minutes, the plane flying at about 3,0000 ft. (900 m.). The temperature inside the plane was well over 100° F. (37.8° C.). Half-way through the journey I experienced a burning sensation on my thigh which grew steadily worse. I felt that the other four passengers might be alarmed if I removed my trousers, and exercised self-restraint until the plane landed. I

was first off the plane, ignored the greetings of a colleague who had come to meet me, and travelled at high speed to the lavatory. By that time I had a bright red patch, two inches (5 cm.) in diameter, on my thigh, and the burning was intolerable. Subsequently a bleb formed in the centre of the patch, and the lesion, although protected, took about a week to heal. I thought at first it was a particularly vicious insect bite, but then realized I had been carrying a petrol lighter in my trousers pocket.

The following summer, having forgotten the incident, I made precisely the same mistake and developed another vapour burn on a similar journey. No doubt the high temperature and lowered pressure aided the production of the burns. I am confident that they were due to vapour alone, as there was no petrol leaking from the lighter. It is fortunately an accident unlikely to happen in England. Occasions when we travel in our shirt-sleeves by air are unusual.—I am, etc.,

Keighley and District Victoria Hospital, Keighley. IAN STEWART.

SIR,—Among the many fascinations of pathological work in West Africa are the odd ways in which people there contrive to kill themselves and each other. I was reminded of one such by Dr. R. W. Ainsworth's case of petrol-vapour poisoning (May 21, p. 1547).

At Cape Coast (Ghana) in 1947, a male aged about 24 went to bed in an inner room without a window. When in the morning he did not appear or respond to calls, the door was broken down and he was found dead. It appeared that, sleeping on the floor as they do, he had kicked over a part-full 4-gallon petrol tin, the hole, as usual, merely closed with a little bit of rag. So far as I remember the post-mortem appearances were as described by Dr. Ainsworth.—I am, etc.,

Bristol. GEORGE L. ALEXANDER.

Smoking and Personality

SIR,—In the paper by Professor H. J. Eysenck and his co-workers (May 14, p. 1456) the authors quote criticism which shows the logical fallacy of postulating a causal relationship between smoking and lung cancer, only to associate their own conclusion with a similar logical fallacy.

The criticism of Fisher[1] and Berkson[2] and others is quoted. This threw doubt on the idea that statistical relationship between smoking and lung cancer implied a causal relationship on the grounds that alternative and equally plausible theories existed and had not been disproved—that is, that both rate of smoking and proneness to lung cancer are due to some third variable underlying both. The authors set out to show that this underlying and third variable is the individual's genotype. As evidence to strengthen the hypothesis they constructed personality inventories to elicit the personality trait of "extraversion," "rigidity," and "neuroticism," and correlated these with the smoking habits of 2,360 males. They found a strong correlation between cigarette smoking and "extraversion" and a weak correlation with lack of "rigidity." The authors concluded that: "On the whole the data confirm the view that genotypic differences exist between smokers and non-smokers."

Here they fail to consider at least one alternative and equally plausible theory which has not been disproved, that not the genotype, but the cigarettes themselves, containing, for example, nicotine, a drug acting on the nervous system, may be responsible for the personality differences. The authors' figures might be used to support either theory impartially. It is interesting to note that in the trait score for "extraversion" the mean scores for smokers were 7.133, 7.445, and 7.805 for light, medium, and heavy smokers respectively. Should "extraversion" be affected by cigarette smoking, one might expect a decreased score in ex-smokers, and a mean score of 7.27 is in fact quoted for this group, as compared with a mean of 7.016 in non-smokers. This might support the alternative hypothesis, or again be due to the fact that the former smoking habits of the ex-smokers were not comparable with those of the present smokers. Again, the difference may not be significant, but on all these points the authors elect not to comment. To summarize, the evidence presented does not, as the authors claim, confirm the view that genotypic differences exist between smokers and non-smokers, and the figures given might equally well support an alternative hypothesis.—I am, etc.,

St. Mary's Hospital, London, W.2. FRANK F. RICHARDS.

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Dangers of Halothane

SIR,—The letter from Drs. G. Langton Hewer and R. I. Ballantine (March 19, p. 876) details three cases where cardiovascular collapse was attributed to halothane administration via a semi-closed circuit. Dr. H. Rex Marrett's comment (April 16, p. 1208) on Case 1 that administration of thiopentone and lignocaine in a patient with a known precarious cardiac condition may have played a part in the collapse prompts us to record a similar case where these features were absent.

A woman of 68 was anaesthetized for reduction of a Colles fracture sustained in a fall the previous evening. There was no history of cardiovascular or respiratory disease. On examination she was slightly obese and her blood pressure was 160/90 mm. Hg, but no other significant abnormality was detected in cardiovascular or respiratory systems, and the urine was normal. Atropine 0.6 mg. was given one hour before induction. Anaesthesia was induced with nitrous oxide and oxygen. With 6 litres/min. of nitrous oxide and 2 litres/min. of oxygen, halothane was added from a calibrated vaporizer, starting with 0.5% concentration, going up to 3%, reduced to 2% for maintenance. At no stage was the patient allowed to become cyanosed. Pulse had shown no marked reduction in rate or volume and respiration was satisfactory. About 15 minutes after commencing the anaesthetic a simple reduction of the fracture had been accomplished, and a plaster slab was being applied. Signs of collapse then developed, the patient becoming pale and slightly cyanosed. The pulse became grossly irregular, rapid, and of poor volume. The apex rate was about 120 beats/min. and there was an apex-wrist deficit of 20–40 beats/min. Blood pressure fell to 70 systolic and respiration became shallow. The airway was checked, the anaesthetic discontinued, and the lungs inflated with pure oxygen. The patient's condition rapidly improved, the pulse became stronger, and she recovered consciousness after a short while. Her blood-pressure was then 150/90 and her condition perfectly satisfactory apart from occasional bouts of cardiac irregularity, which persisted for some 15 minutes. Subsequent progress was closely observed but was quite uneventful. An E.C.G. taken an hour later was within normal limits. The patient has remained well.

This case supports the view that, though such incidents are rare, relatively small amounts of halothane can cause cardiac irregularity in apparently fit patients. We are, etc.,

Bethnal Green Hospital, London, E.2. H. J. GALVIN.

Hammersmith Hospital, London, W.12. D. F. HAWKINS.

Complications of Asbestosis

SIR,—I read with much interest the report of the clinicopathological conference on the "Complications of Asbestosis" (April 30, p. 1345). While the case presented had so many instructive facets, I was a bit worried about the diagnosis of the valvular lesions in the heart. The heart signs that the patient had were "a Grade 3 aortic systolic murmur and an accentuated pulmonary second sound with an opening snap and mid-diastolic murmur at the apex," and the clinical diagnosis made on the heart lesions was "'quiescent' aortic incompetence and mitral stenosis." I thought that the diagnosis of aortic incompetence was obviously incompatible in the absence of an early diastolic murmur anywhere in the praecordium, whereas a Grade 3 aortic systolic murmur could be easily compatible with aortic stenosis.

The post-mortem report, however, did not reveal any aortic stenosis (from circumferential measurements), but the lesions described in the aortic valves could be taken to mean that the valves could be incompetent during life. Further, the Grade 3 aortic systolic murmur could not be explained by such lesion unless one supposed that there was some altered haemodynamic (so-called "dynamic stenosis") during life or that the mild atherosclerotic lesion had something to do with the production of the systolic murmur.—I am, etc.,

Edinburgh, 3. S. K. SEN.

High-pressure Salesmanship

SIR,—May I, as an erstwhile member of the medical profession and now one who has been engaged in advertising for 24 years, be allowed to offer my deep sympathy to those of your readers who have been bogged down by mailing shots and by those pharmaceutical organizations who have been pestering them with questionaries in the cause of what they are pleased to call "market research"? I have had a very considerable experience of medical advertising on both sides of the fence and I am still utterly amazed by the persistence with which some quite reputable drug manufacturers bombard the profession with leaflets, pamphlets, booklets, and even free samples that the hard-working G.P. has neither the time nor the inclination to explore.

If and when a new drug does arise, surely it is enough to announce and repeat the fact in the pages of the *Journal* and other professional periodicals? I know for a fact that these journals are read through from cover to cover by a large percentage of practitioners. I know also that they constantly give fair editorial consideration to many new products. And I have yet to hear of a doctor who consigns them immediately to his wastepaper basket.

As for market research, pure and simple, let us not perhaps be too hasty in our condemnation. Many qualified medical men are now assisting the leading advertising agencies in this respect, and getting good fees for their services. But—as a certain psychiatrist said to me only a few days ago—really effective market research lies not so much in badgering people to answer questionaries as in using one's own good common sense. —I am, etc.,

London, W.1. J. BUNTING.

Grey Turner Lecture

SIR,—In my Grey Turner lecture on surgery of the oesophagus, published in the *British Journal of Surgery* (1960, **47**, 457), I mentioned that the first surgeon to resect the oesophagus was Czerny. Unfortunately I find that the portrait (Fig. 448) is that of Professor Adalbert Czerny, of Berlin, while the surgeon who first resected the oesophagus was Professor Vinzenz Czerny, of Heidelberg.

My informant is Professor F. Stelzerner, of Hamburg, who sends a photograph of Professor Czerny of Heidelberg. Unfortunately the only thing I can do now is to apologize for the error.—I am, etc.,

London, W.1. HENEAGE OGILVIE.

POINTS FROM LETTERS

Internal Tampons

Dr. PAULA H. GOSLING (Royal East Sussex Hospital) writes: The external or distal end of an internal tampon is blood-stained long before the internal two-thirds are saturated, and I cannot see how this can be explained with the mild or moderate flow of mid and late menstruation, except by capillary flow in the tampon. The purpose of both tampons and sanitary towels is to absorb the menstrual flow, but tampons are far more efficient; partly because they are applied nearer the source, partly because the material of which they are made seems to be more absorbent. If tampons acted by merely damming the flow, as Mr. E. Broughton Barnes (April 2, p. 1057) seems to imagine, the apparent duration of menstruation (i.e., the number of days for which protective clothing is necessary) would be the same as with towels, instead of being approximately one day shorter, as it is in fact.

Psychotherapy in Migraine

Dr. G. C. PETHER (Hitchin) writes: Drs. Richard A. Hunter and Ian P. Ross (April 9, p. 1084) describe the value of psychotherapy in migraine. They state that some of their male patients only had attacks at the week-end when at home. E. Neuwirth (*Ann. Intern. Med.*, 1952, **37**, 75) describes cervical diskopathy producing, among other symptoms, a condition closely resembling migraine. I had a patient recently who found that his week-end pain was due to excessive digging and garden work. Very possibly his trouble was linked with cervical diskopathy. . . . If psychotherapy fails in some of these cases, may it not be that the condition is essentially organic and that the patient has been rather unfairly labelled?

Shoes for Children

Dr. MARGARET EMSLIE (London, S.W.) writes: Mr. T. T. Stamm (April 30, p. 1367) should not put words into my mouth. I have never said that "all that is necessary" is to design children's shoes properly, nor have I thought it.

Reed-Sternberg Cells

Dr. J. B. GURNEY SMITH (Redhill, Surrey) writes: I observe an article (April 23, p. 1239) relating to the so-called Reed–Sternberg cell in Hodgkin's disease. One would hope the correct name would now be in use. I recall, as an old clerk at Bart's to the late Dr. A. E. Gow, who was an authority on this disease, that he would insist on these giant cells being called Andrewes's cells. It is a fact, I believe, of medical history that Sir Frederick Andrewes, F.R.S., of Bart's, was the first to describe these cells.

Obituary

WILLIAM MOODIE, M.D., F.R.C.P., D.P.M.

Dr. William Moodie, consultant physician to the department of psychological medicine at University College Hospital, and consultant (emeritus) to the London Child Guidance Training Centre, died suddenly on May 24 at his home in London. He was 74 years of age.

William Moodie was born on March 13, 1886, the only son of Robert Moodie, of Arbroath. From Arbroath High School he went on to study medicine at the University of St. Andrews, graduating M.B., Ch.B. in 1908, and proceeding M.D. in 1914. After qualification he became assistant to the professor of physiology at the University College, Dundee, for three years, and then transferred to the department of pathology. Coming to London in 1913, he entered the mental hospital service of the London County Council. During the first world war he served in the R.A.M.C. as a specialist in pathology, and he went, with a regular commission, as a member of the North Russian expedition in 1919. On demobilization he returned to the mental hospital service. He took the D.P.M. of the London University in 1921, the M.R.C.P. in 1923, and he was elected F.R.C.P. in 1934. He was for a time deputy medical superintendent of the Maudsley Hospital.

He joined the staff of University College Hospital as assistant physician in the department of psychological medicine, and when he retired ten years later he was appointed consultant physician. For many years he was director of the London Child Guidance Clinic—now a Child Guidance Training Centre—and his best-known publications were concerned with child psychiatry. His book *The Doctor and the Difficult Child* was published in 1940. It was followed in 1945 by *The Doctor and the Difficult Adult*, and in 1946 by *Child Guidance*. During the second world war he again served in the R.A.M.C., this time with the rank of lieutenant-colonel, as a specialist physician.

In 1922 he married Mary Enid Hardy, who survives him, together with two daughters.

Dr. KENNETH SODDY writes: William Moodie's career can be divided into three parts, during the most important of which he, more than anyone else, was responsible for the introduction of child guidance to this country. Before this, however, he had built himself a considerable reputation as a physiologist, clinical pathologist, and, later, neuropathologist. The third part of his career was his service in the R.A.M.C. as medical officer, general duties, in the first world war, and in the second world war as a medical specialist, having remained on the Territorial Army Reserve of Officers between the wars. At the age of about 56 he served right through the siege of Tobruk, being evacuated just before the fall, and followed this with a long period in Gibraltar, a record of service that undoubtedly took a great deal out of him.

Moodie was a very practical-minded man with a keen interest in mechanical gadgets, a certain impatience with theory, and a strong sense of social responsibility. In most ways he was an ideal choice for the Commonwealth Fund of America to send on a fact-finding tour of the United States in 1927 with a view to introducing child guidance to the United Kingdom. His open-mindedness to new practical ideas, his desire to be of service, and his acceptability to more orthodox-minded professional colleagues gained a good measure of support for the London Child Guidance Clinic which was established in 1929 in order to pioneer a child-guidance service, together with providing the appropriate postgraduate training.

Perhaps Moodie's most important contribution was the interpretation of the new technique to the medical profession and to the responsible public. Doctors in particular trusted him because of his qualifications and past medical record and for his insistence on practical values rather than theoretical speculation. If Moodie scarcely advanced the theoretical basis of his subject, he successfully created opportunities for others to do so.

His combination of qualities and experience made him a good choice for the reorganization of the department of psychological medicine at University College Hospital after the war, where he pioneered the adequate representation of child psychiatry in the medical students' curriculum. He believed not so much that this subject was important in itself to the student, but rather that it contributed a unique illumination to the social aspects of medicine.

Repeated coronary thromboses restricted his activity considerably in the last seven years of his life, but he retained many interests, and in particular was prominent in the field of medical hypnosis, a technique which appealed to him because of its very practical but rather restricted nature.

As a personality, Moodie was diffident and shy, and his self-deprecating manner to some extent prevented the recognition of his contribution to society. In fact, few doctors of his generation did more than he to alter the shape of medical practice. The whole principle of interdisciplinary teamwork, in which doctors work on terms of equality with members of other relevant professions was introduced to medical practice through child guidance. Moodie was unobtrusively insistent on the value of interprofessional co-operation, but now that this has become an accepted commonplace in a number of medical fields the early difficulties and opposition to such ideas are generally forgotten.

A. E. W. IDRIS, F.F.A. R.C.S.

Dr. A. E. W. Idris, formerly senior consultant anaesthetist to the Middlesex Hospital, died on May 21, in his 71st year.

Arthur Ernest Williams Idris was born on September 9, 1889, and in 1908 he entered the medical school at University College Hospital, from which he qualified in 1913. After holding house appointments at the old Great Northern Hospital and at Queen Mary's, Stratford, he joined the R.A.M.C. in 1915. A wound he received while on service left him slightly lame.

After the war he became interested in anaesthesia, and his aptitude for this specialty was recognized by his appointment in 1922 as assistant anaesthetist to the Middlesex Hospital, where he had previously been resident anaesthetist. Appointment to many other hospitals soon followed; these included the National Dental, the Queen's at Sidcup, the Ministry of Pensions Hospital at Orpington, the Hostel of St. Luke, and the Hampstead General. Meanwhile he had become anaesthetist to the dental department at the Middlesex in 1927, before his promotion to the full honorary staff of that hospital in 1931.

The demands of his private practice forced him to resign from many of these posts, but he was never too busy to attend St. Luke's Hostel for the Clergy, and he retained a deep affection for the Hampstead General, which he served for the rest of his professional life, becoming senior anaesthetist there after the second world war.

At the Middlesex he was an early practitioner of endotracheal and intravenous anaesthesia, and was largely instrumental in introducing anaesthetic machines into routine use. Imperturbable in the operating theatre, he was much in demand for very major surgery in bad-risk cases, with which he was at his best, while in routine work his dexterity at the rapid induction of inhalational anaesthesia was widely appreciated.

A member of the Anaesthetic Section of the Royal Society of Medicine since 1924, he became a Founder Member of the Association of Anaesthetists in 1932, a Fellow in 1946, and a Senior Fellow in 1955. Granted the Diploma in Anaesthetics in 1935, he was elected F.F.A. in 1948.

With the dispersal of the hospital services in the second world war, he was posted to the E.M.S. sector hospital at Tindal House in Aylesbury, but at the conclusion of hostilities he returned to the Middlesex Hospital, where he became

senior anaesthetist in 1946. In 1950 he was appointed consultant anaesthetist to the Ministry of Pensions.

In 1954 he retired from his hospital appointments and from active practice, and devoted his attention to the garden of his home on the Thames near Abingdon, and to his collection of antique furniture. His knowledge of this subject was great, and he was in fact an expert carpenter and cabinet-maker. In 1936 he was involved, through no fault of his own, in an explosion and fire in an operating theatre, and was not only badly burnt, but his long-standing deafness was exacerbated. The latter disability became severe towards the end of his career, and in consequence he tended to avoid committees and other professional meetings.

To his juniors Ernest Idris gave unbounded encouragement and loyal support, and both they and the many generations of Middlesex students, to all of whom he was always affectionately known as "Pop," will gratefully remember his kindness, his warm humanity, and his unfailing good humour.

He is survived by his widow, to whom we extend our sympathy.—O. P. D.

C. J. M. D. writes: I would like to add my tribute to the memory of my old teacher, colleague, and friend, A. E. W. Idris. Bred in the chloroform era, he was one of the first to emerge from it by the introduction of Boyle's apparatus, and later he was the first to use the intravenous anaesthetic "pernocton." He never refused to anaesthetize a case however desperate, and he was imperturbable in the face of difficulty. He had the supreme virtue of delegating cases to his juniors early in their careers, thus giving them invaluable experience. Known to us all as "Pop," we—to him—were collectively known as "Laddie." His genial, rubicund countenance inspired affection and confidence in students and patients alike, and his colleagues will sorely miss him.

D. C. WILSON, M.D., F.R.C.P.Ed.

Dr. D. C. Wilson, consulting physician to the Northern Regional Hospital Board, died suddenly on May 9 while at work in the Royal Northern Infirmary, Inverness. He was 63 years of age.

David Cook Wilson was born in Fife on March 15, 1897. Educated at Edinburgh Academy, he began his medical studies at Edinburgh University just before the first world war. Early in 1915 he was commissioned in the Black Watch, and, while serving in France, was twice wounded. After demobilization he resumed his studies in Edinburgh and graduated M.B., Ch.B., in 1921. After holding the post of house-surgeon in Leith Hospital he joined his father in general practice in Anstruther. Admitted to the Royal College of Edinburgh as a Member in 1931, he was elected a Fellow in 1938. During part of this period he was president of the Royal Medical Society of Edinburgh.

While engaged in medical practice he was a keen member of the R.N.V.R. and wore the V.R.D. At the commencement of the second world war he was mobilized and posted to Egypt, where he served for over two years. For his excellent work there he was mentioned in dispatches. At the end of the war, he was in charge of the Northness Royal Naval Base Hospital, Lyness, Orkney, holding the rank of surgeon-commander.

In 1945, still steeped in his study of medicine, he proceeded M.D. at Edinburgh University, and shortly afterwards took over the practice of the late Dr. R. D. Campbell, of Inverness. When the National Health Service was launched in 1948 he became consultant physician to the Northern Regional Hospital Board, making rheumatism his special study, and in the treatment of this distressing ailment he showed a high degree of skill and knowledge. During his period in Inverness he served for six years on the Northern Regional Hospital Board, and at the time of his death was chairman of the executive council for the County of Inverness. A member of the Scottish Committee of the B.M.A. for a number of years, he had also been chairman of the Inverness Division.

W. T. B. writes: It was with deep sorrow that both medical and lay circles in the Highlands heard of the sudden death of David Wilson. Earlier this year he had been laid low with a coronary thrombosis and had just returned to light duty. An outstanding Scot, he was a man of sterling character, of profound wisdom, common sense, and tact, all of which were tinged with humility, which made those assets all the greater. His work as a general practitioner gave him that extra experience that counts so much in a consultant. His skill in the office of chairman of the executive council was quickly recognized, and his valuable help in administration will be greatly missed.

He was a man whose friendship we all valued very highly, a man whom we all loved. He leaves a widow and two grown-up sons, and the deep sympathy of their many friends goes out to them in their great loss.

H. J. FULLER, M.R.C.S., L.R.C.P.

Dr. H. J. Fuller, who practised at Wadhurst, Sussex, died suddenly on May 18, aged 63.

Harold John Fuller was born on July 5, 1896. Educated at Westminster School, he left to join up in the first world war, serving in the Queen's Westminsters and later as a pilot in the R.F.C. Severe concussion in a crash, almost inevitable in those days, checked his flying career only for the length of convalescence. He returned to flying duties with the same calm determination which characterized his subsequent life. The war over, he entered Guy's and qualified from that hospital in 1924. Shortly afterwards he joined a partnership in Wadhurst, Sussex.

A. H. D. writes: The death of Dr. Harold Fuller means the loss of a man whose life exemplified those qualities which have made our general practitioners an object of admiration throughout the world. His success in general practice was the result of skill, judgment, true friendliness to his patients, a quiet sense of humour, and unfailing courtesy and kindness. He strictly observed the ethical code of his profession and had the courage to castigate others who lacked his integrity. His work was interrupted by the second world war, in which he served with the R.A.F. After demobilization he returned to general practice, but suffered a severe coronary thrombosis in 1951. Completely undeterred by the disease, he was soon back again, cheerful, uncomplaining, and as dedicated to his patients as ever. He set an example in his domestic and professional life to which few can aspire but all can praise. He was devoted to his wife and children, and their grief is shared by his patients and colleagues in all branches of his profession.

Sir ROBERT McCARRISON, C.I.E., M.D., D.Sc. LL.D., F.R.C.P.

The obituary of Sir Robert McCarrison was published in the *Journal* of May 28 (p. 1663).

N. C. P. writes: Those of us who were fortunate enough to be associated with Sir Robert McCarrison in his work at Oxford after his retirement from the I.M.S. have lost a beloved colleague and friend. His absolute sincerity and integrity coupled with his dislike of publicity immediately commanded our respect, and his kindly interest in other people's affairs and his love of young people endeared him to all, especially those who were fortunate enough to meet him and his wife at their home in Linton Road.

It was his absorbing interest in the welfare of the rising generation in general and of doctors in particular that made his work as director of postgraduate studies at Oxford such a satisfaction and pleasure to him. In 1948 he wrote, "The longer I live, the more I admire the young folks. . . . The older I grow, the younger in mind and feeling, though not in body, I am when I'm with these young people, and many of them, bless their hearts, think it is worth while to look in upon us."

His natural dignity, without any trace of pomposity, made him an ideal chairman of the Medical War Committee and of the combined meetings of the B.M.A. and the American

Army medical staff. The smooth working of the Medical War Committee was due to his skilful and sympathetic approach, and that of his old friend and colleague, Dr. Lupton, the honorary secretary. Those who served under him in his capacity as regional adviser in medicine to the Emergency Medical Service found him always ready to help and full of resource.

During his later years, when his sight and heart began to fail, he bore his troubles with a smile, helped by the constant and loving care of his wife. He was profoundly thankful to be able to celebrate their golden wedding, and had previously written one Christmas, "This brings our festivities to an end, and we hope to have New Year's day alone, one of those quiet 'days for two' which still beat all others, even after 42¼ years of married life."

Oxford medicine was indeed fortunate in the two wars to have in its midst two such men as Robert McCarrison and William Osler.

Medico-Legal

STAR CHAMBER METHODS IN ADOPTION CASES

[FROM OUR LEGAL CORRESPONDENT]

On his last appearance in Court before his retirement, on the last day of the Hilary Term, April 13, Mr. Justice Roxburgh made reference to two adoption appeals from juvenile courts heard by him earlier in the term (*The Times*, April 14). His Lordship stated that he had used strong terms in those cases because he saw in them departures from the fundamental principle of English law that a parent should not be deprived of his parental rights against his will except upon sworn evidence and with knowledge of the charges against him. Unfortunately, he had no reason to suppose that the procedure in those cases was exceptional.

Natural Parents' Consent

By Section 4 of the Adoption Act, 1958, no adoption order can be made without the consent of the parents or guardian of the child. By Section 5, the court is empowered to dispense with this consent if it is satisfied that the person whose consent is to be dispensed with has abandoned, neglected, or persistently ill-treated the infant, or cannot be found, or is incapable of giving his consent, or is withholding his consent unreasonably, or has persistently failed without reasonable cause to discharge the obligations of a parent or guardian. The two appeals referred to concerned the exercise by juvenile courts of the power to dispense with the consent of one or both parents. In each case, Mr. Justice Roxburgh strongly criticized two matters, one of them concerning the Adoption Rules, and the other concerning the practice adopted by the magistrates in the hearing of the applications.

Where an application is made for an adoption order, under the Adoption Rules, notice of the application must be given to the parents. But the Rules do not require that that notice shall contain a statement that the applicant proposes to ask the Court to dispense with any consent where that is the case. This is clearly unfair. Many parents are not aware that their children cannot be taken away from them without their consent. Even those who are aware of this should receive notice of the intended course of action so that they can prepare to meet the applicant's case on the matters which must be proved before the parents' consent can be dispensed with. His Lordship pointed out this grave defect in the Rules.

Misuse of Children's Officer's Report

The other main cause for complaint in the two appeals concerned the use made by the magistrates of the children's officer's confidential report. His Lordship stated that the purpose of these reports was to enable the magistrates to be satisfied that the adoption would be for the benefit of the child. As long as they were used for that purpose their existence could not be criticized, but in these cases they had been called into use as proof of the matters required by Section 5 as conditions precedent to dispensing with the parents' consent. Used for that purpose they were most objectionable, since they were not on oath and were not admissible in evidence, as they consisted largely of hearsay. Mr. Justice Roxburgh stigmatized this use of the secret reports as a Star Chamber method.

The Two Appeals

Case 1

The first of the two cases was an appeal from an adoption order made by the Gravesend Juvenile Court, after dispensing with the parents' consent to the adoption of their 6-year-old son by a Gravesend couple. The appeal was heard on March 23 (*The Times*, March 24). The appellant was the father, who was serving a three-year sentence in Pentonville Prison for theft at the time of the appeal. The magistrates made the adoption order on October 27 although the mother had withdrawn her consent, and although the husband had written from prison saying that he wished to oppose the adoption and wished to be heard. He asked several times if he could attend court, but was told that he would have to wait until the court sent for him. He was notified by the clerk of the court the day after the hearing that the order had been made. The magistrates had purported to dispense with his consent on the ground that he had persistently failed to fulfil his obligations as a parent.

On appeal it was held that the magistrates had dispensed with consent on no evidence, since they relied exclusively on the children's officer's confidential report; moreover, the parents were not told of the case against them. The report stated that the child's father had been in and out of prison. British justice would not allow that sort of allegation to be made in secret. Although the mother was now once more willing to give her consent, as she had not the means to keep the child, the Court allowed the father's appeal, and the parties agreed to a new trial before other magistrates at Gravesend. In allowing the appeal, Mr. Justice Roxburgh said that this would cause some hardship to the adoptive parents, but not necessarily permanent hardship, and it was important to allow the appeal to establish a point of principle.

Case 2

The second of the two cases was an appeal from the refusal of the justices of the City of Liverpool to make an adoption order in respect of a 5-year-old boy. The appeal was brought by the proposed adopters and was heard on March 24 (*The Times*, March 25). In this case the appeal was not allowed, because the magistrates came to the right conclusion though they travelled by a most reprehensible route. Having considered the children's officer's confidential report improperly, they found that the matters there disclosed did not show that the parents were withholding their consent unreasonably. Mr. Justice Roxburgh strongly disapproved of the course taken by the magistrates, since they made it clear that had the secret report been in other terms they would have been prepared to dispense with the parents' consent on the strength of it.

The application to the magistrates did not ask them to dispense with the parents' consent, for at the time of application they did consent. This consent was withdrawn before the hearing before the magistrates. The clerk to the justices apparently thought, wrongly, that the burden was on the parents to explain why they withdrew their consent, and invited them to give evidence on oath. After the parents had given evidence and been cross-examined, the secret report of the children's officer was read out: the proposed adopters gave no evidence of the matters set out in Section 5 of the Act, although the burden was upon them to prove one or more of those matters. The report was apparently treated as though it were their evidence. The reading of that report in itself was objectionable: what made matters even worse was the fact that it was read after the parents' evidence was closed, so that they were unable to deal with any allegations made in it.

CORONERS' CASES

Easy to Criticize Afterwards

A doctor was criticized, at a Sunderland inquest, by the husband of a woman who died in the General Hospital of peritonitis due to appendicitis. It was stated that the patient, Mrs. Appleby aged 47, complained of abdominal pains on

March 13. The doctor was alleged to have made an inadequate examination, in consequence of which he diagnosed jaundice instead of appendicitis. The patient's condition deteriorated, and, after she had been seen by her doctor a number of times, she was admitted to hospital. An emergency laparotomy revealed peritonitis and appendicitis. She died early the next morning, a fortnight after her illness began.

Dr. V. R. Nair, senior house officer at the General Hospital, gave evidence that the correct diagnosis was only made at operation. "It would have been very difficult for anyone to make a diagnosis from an external examination," he said. No trace of jaundice was found, but the deceased could have recovered from this. The coroner, Mr. C. Morton, remarked that if the doctors at the hospital were unable to make an exact pre-operative diagnosis it would be very difficult for the general practitioner to do so. Expressing his satisfaction with the medical evidence, he said, "It is easy to criticize after the event. The doctor did his best to diagnose the complaint." A verdict of death from natural causes was recorded (*Yorkshire Post*, March 31).

Medical Notes in Parliament

SUBPOENA POWERS RESTORED TO PROFESSIONAL TRIBUNALS

[FROM OUR PARLIAMENTARY CORRESPONDENT]

The Government having announced their acceptance in principle of the recommendations of the Simonds Committee on subpoena powers for professional disciplinary tribunals, the only question left open when the Professions Supplementary to Medicine Bill came before the House of Lords on May 30 was whether these powers were to be restored to the tribunals which the Bill establishes. The answer was given in the announcement by Lord ST. OSWALD, the Government spokesman, moving the second reading of the Bill, that after the Whitsun recess Government amendments would be moved to restore the express power for the issue of writs which was struck out of the Bill during its passage through the Commons. Lord TAYLOR, for the Opposition, welcomed the decision, expressing his full agreement that it was necessary for the disciplinary committees to have this power. If there were to be professional inquiries, he said, then there must be power to get the evidence to make the inquiries realities.

Formidable Penal Powers

Viscount SIMONDS, a Lord of Appeal, who was chairman of the Departmental Committee on Powers of Subpoena of Disciplinary Tribunals, whose report was published on May 20,* took part in the debate. The Bill, he said, would establish disciplinary committees with formidable penal powers to deprive a member of any one of the professions of the right of earning a livelihood in his chosen profession. It was true that, though removed from the *Register*, he could still practise, but nobody would doubt that his chances would be greatly marred and his reputation would suffer. What would be the position of a member of a profession, charged with an offence which might result in serious consequences, who knew that there was evidence available if the witnesses would come forward, and which if given might turn events in his favour? Beyond all doubt, there should be power to compel such witnesses to come forward. What also was the position of a man charged whom the prosecution, whose interest was to maintain the honour of their profession, thought was not fit to practise and yet who continued to practise it to the detriment of the public? They might have information which led them to believe that such a man was not fit to practise, but might find that the evidence they relied on was not forthcoming. There was also the point of view of the disciplinary committee, which was exercising a judicial function, faced with a plea from one side or the other, "If only there was evidence I could convince you." It might be true or it might be false, but what was the committee to do except to decide on the evidence that was before them, and come to a decision which they must know they might not have reached otherwise? Everything demanded that with a tribunal of this kind the evidence should be available, otherwise justice was not done.

*See *British Medical Journal*, May 28, p. 1666.

Police Evidence

Some misunderstanding had arisen about the last words of the report which had been thought to have something to do with telephone tapping. Of course it had nothing to do with that. The question was whether a policeman, like any other man, should be amenable to the jurisdiction of the court and compelled to give evidence of matters which had come under his personal observation. Of course he should. The policeman was nothing but a citizen in uniform. That did not mean that in any sense the police authorities had to volunteer information to professional bodies, or that even if asked that they must give it. It meant that if a policeman had seen or heard something material he should be able to be compelled to tell the tribunal what he had seen or heard. He hoped there would be no qualification of any kind when the subpoena provision was inserted in the Bill.

Lord SILKIN said Lord Simonds had complained about misunderstanding of the last words of his report, but there was a certain amount of apprehension about police evidence, particularly police evidence obtained by tapping telephones. There had been a case where a member of a profession was struck off the *Register* almost entirely on evidence obtained by the police tapping telephones.

Viscount SIMONDS: If Lord Silkin is thinking of the same case as I am, it was not a case of telephone-tapping at all. But it is a case shortly coming before the judicial committee of the Privy Council and therefore I was careful not to say anything about it. Lord SILKIN said he would not say anything more about that particular case, but there was a general abhorrence of any evidence obtained in that way. While it might be that Lord Simonds's report did not specifically deal with this question, it should be ensured somehow that such evidence was not acceptable or given by police witnesses in cases of hearings on discipline.

The Bill was read a second time.

ADOPTION ACT AMENDMENT

[FROM OUR PARLIAMENTARY CORRESPONDENT]

Removing Flaw in Legitimation Procedure

A Bill to enable revocation orders to be issued (when so requested) in all cases where a child is legitimized, and not only those under Section 26 of the Adoption Act, 1958, was given a first reading on May 24. Mr. J. PARKER (Dagenham, Lab.) obtained without dissent leave to introduce the Bill, which he explained was to close a gap in the Adoption Act disclosed by the passing of the Legitimacy Act last year. If a father or mother alone adopted a child who was illegitimate and subsequently married the other parent the child could be legitimized because the adoption order could be revoked. But if the father and mother jointly adopted a child the adoption order could not be revoked if there was a subsequent marriage of the parents and they sought to legitimize the child in that way. This was an unfair discrimination against a small group of people who had hoped to benefit from the provisions of the Legitimacy Act. The birth certificate with the word "adopted" on it could not be withdrawn and an ordinary certificate issued. The Bill, as Mr. PARKER reminded the House, has the good will of the Home Secretary and the promise of his assistance in its passage.

ROYAL COLLEGE OF PHYSICIANS

The Royal College of Physicians of London Bill was read the third time in the Commons on May 30.

QUESTIONS IN THE COMMONS

Local Authorities' Share in Hospital Administration

Mr. H. DELARGY (Thurrock, Lab.) asked the Minister of Health on May 24 whether he would amend the National Health Acts so as to provide for the representation of local authorities on regional hospital boards and group management committees. Mr. D. WALKER-SMITH refused, but added: I regard local authorities as a valuable source of advice about appointments to these bodies. Local health authorities are always consulted, and many members of local government bodies do also serve as members of regional hospital boards and hospital management committees.

Non-smoking Wards in Hospitals

Dr. ALAN THOMPSON (Dunfermline, Lab.) asked the Minister on May 27 if he would examine the possibility of providing separate wards in hospitals for non-smokers in order to protect bronchitic and asthmatic patients. Mr. WALKER-SMITH stated that it was within the discretion of individual hospital authorities to decide what arrangements should be made regarding smoking, and he was sure they would be vigilant to protect patients who found tobacco-smoke objectionable; one must, however, bear in mind that many bronchitic patients were confirmed smokers.

Road Accidents: Safety-belts

Mr. D. JAMES (Brighton, Kemptown, Con.) asked the Minister of Transport on May 25 whether he had studied Swedish statistics showing the decline in loss of life that followed the fitting of diagonal safety-belts to the front seats of cars, and whether he would consider ways and means of popularizing these methods in the United Kingdom. Mr. JOHN HAY, the Parliamentary Secretary, reminded him that the British Standards Institution recently agreed a new standard for safety-harness. Mr. JAMES suggested that the adoption of safety-harness was a means by which 700 lives could be saved and up to 50,000 serious casualties prevented by immediate administrative action. Mr. HAY said the Ministry were in no doubt about the value and efficacy of safety-belts and types of safety-harness, and were anxious to see more use made of them. The new standard, he added, should be ready for publication about the end of June, and supplies of harness complying with it should be available to the public towards the end of August.

Automatic Suspension of Licence

Mr. H. BOYDEN (Bishop Auckland, Lab.) suggested in a question to the Minister of Transport that he should introduce legislation providing for the automatic suspension of a licence for a year when a driver was convicted of being drunk in charge of a motor-car. Mr. ERNEST MARPLES said he would bear the suggestion in mind in the review he was making of road accidents generally. To this he added that any legislation should be comprehensive and not piecemeal, and asked the House to wait until the Government had considered the whole question of driving and drink.

Dr. ALAN THOMPSON, on another question, said it was many months now since Professor Drew's medical research team demonstrated with complete scientific accuracy that there was now an objective test to assess the influence of drinking and drugs on driving. Would the Minister give an assurance that he would incorporate those findings into the legal system? Mr. MARPLES pointed out that it was not "many months" ago. But this was one of the most important issues. The Government were making an exhaustive analysis before bringing in any legislative proposals, and a joint team from the Home Office and the Ministry of Transport would be visiting Scandinavia soon to see how they coped with drink and drugs. Mr. W. BENN (Bristol, South-East, Lab.) said that unless there was some effective test after accidents it would never be possible to find out how many were due to drink and drugs. Was the Minister proposing to introduce any tests which could be applied to give the diagnostic figures he needed before he could act? Mr. MARPLES thought it better to wait till the Government had completed their study.

Damages Clause in Policies

Mr. C. OSBORNE (Louth, Con.) made the suggestion that a common policy should be devised to make the guilty driver in a road accident bear the first £25 of the cost of any accident and the first £50 of third-party compensation. Mr. MARPLES was not satisfied that the suggestion in this form would not involve the possibility of serious injustice to injured parties. He proposed to discuss the whole question of road safety with representatives of the insurance companies and underwriters. Mr. OSBORNE pressed the point that if in some way the guilty party could be made to pay it would have some effect in stopping accidents. Mr. MARPLES replied that to determine who was guilty often cost a great deal of money. Lawyers were an expensive luxury. Therefore it was difficult to apportion the blame. In his opinion a cash fine was not a deterrent; it was less effective than suspension of the driving-licence.

Comparative Accident Figures

Lieut.-Cmdr. L. MAYDON (Wells, Con.) collected the following comparative statistics from the Ministers concerned: During 1959 there were 6,820* deaths due to accidents in the home in England and Wales, and 5,916 due to accidents on the roads (289 of them in Wales). In Scotland the corresponding figures were 1,088 at home and 603 on the roads. (*Provisional figure.)

Universities and Colleges

UNIVERSITY OF DUBLIN

SCHOOL OF PHYSIC, TRINITY COLLEGE

The following degrees were conferred on May 19:

M.D.—P. G. S. Beckett.
M.CH.—R. B. Brenan.
M.B., B.CH., B.A.O.—A. A. Barclay, D. Crookenden, P. J. Reid, S. Steinberg.

UNIVERSITY OF LONDON

The degree of M.D. was awarded to A. K. Thould on April 5, and to B. G. B. Christie and N. R. W. Wynn-Williams on April 26.

The following candidates have been approved at the examination indicated:

THIRD M.B., B.S.—[1 6]Linda F. Courtier, [1 2]P. B. Deverall, [1 5]Sharron H. Gilmour, [1 3]J. D. Hamilton, [1 5]D. R. Harvey, [1 5]M. K. G. Hudson, [1 3]G. A. Hunter, [1 5]C. W. Jamieson, [1 5]Rosemary Khin Zaw, [1 6]C. C. Korvin, [1 4]M. A. Modelski, [1 2]Daphne M. Newman, [1 4]G. M. Rees, [1 5 6]R. E. Robinson, [1 2]Elizabeth Shindler, [1 2 5]E. K. M. Smith, [1 3]P. S. Smith, [1 4]P. J. Watt, J. D. Abell, A. P. Adams, P. L. Agulnik, Claire V. E. Aitken, G. O. Alabi, J. J. R. Almeyda, D. A. Amaso, E. G. Anderson, Shelagh J. Anderson, Rachel J. Anstead, Elisabeth M. Appleby, Jean Arnold, I. H. Bailes, R. Balcon, M. L. A. B. Bancilhon, J. K. Bandoh, M. A. Barnett, J. Barrett, Ann A. Barton, B. Batten, D. M. Beardsmore, Mary H. Bell, S. R. J. Bellamy, Sheila A. Beningfield, C. A. C. Bennett, H. E. Berry, J. Bienenstock, Jean M. Bird, R. C. Birt, G. Blandford, R. H. Bluestone, Gillian Blundell, Isobel J. N. Bradbury, J. S. Brewer, D. R. Brown, Diana C. Brown, F. E. Bruckner, J. P. B. Budgen, Edith M. Buffin, Jill A. Bullimore, C. J. Burns-Cox, M. L. Burr, R. G. Bury, A. B. Byles, Maureen M. Cameron, M. J. Campbell, E. M. Carr-Saunders, Janet R. Carruthers, M. E. Carruthers, J. A. Carter, Margaret E. Cash, Mary L. Cashel, P. G. Cassell, Anne J. Cawthorne, D. N. Challacombe, G. Champion, T. Chard, D. T. S. Chesser, I. D. Chisholm, P. A. Clark, H. MacD. Clink, A. Cohen, Bertha C. A. Coker, T. J. Colbridge, G. P. Coleman, B. R. Collier, C. L. Colton, M. D. Constable, J. R. Cook, D. H. Coombe, A. S. Cooper, Dorothy J. Cooper, P. G. Cope, T. B. Cork, Sheila A. Corrin Helena M. J. Cotter, J. S. Cox, C. S. D. Crane, R. C. Crossman, F. P. Crowe, M. F. Cuthbert, B. N. J. Daily, F. Dastur, M. J. Davie, H. R. Davies, S. de Lange, E. R. Dixon, C. F. Donovan, G. A. W. Dove, Ewa M. Dragowska, M. H. Draisey, B. R. Duncan, M. W. O. Dunwoody, Kathleen J. B. Edwards, Patricia M. Egan, Beryl L. Ellis, Mary Ellis, G. J. M. Erwin, C. E. Evans, G. J. Evans, M. D. Farrar, P. O. Fasan, R. E. Faulkner, G. J. Fellows, J. T. L. C. Fernando, Sally E. Flew, A. M. Fox, Janet K. Gambell, Elizabeth A. Gaze, D. H. Georgelin, H. A. Ghazi, B. E. Gilliver, P. L. Girolami, A. Gletsu, R. A. Goldfinch, Mary C. Goodchild, A. S. Gordon, Sheila E. Gould, R. H. Grace, W. R. Gray, Kathleen Green, R. J. Green, Joan M. Greenway, Mary E. Gregory, J. N. Griffin, J. B. Gritton, R. N. Grüneberg, J. H. Hackwood, R. M. Hadley, J. E. Hale, G. J. Halls, D. M. Harris, Jennifer A. Hartley, J. M. F. Hartley, J. M. Hawkings, Ann E. Haywood, Alethea B. Heal,

Diana P. Heptinstall, R. D. Hill, Clare, Hilton, Pauline B. Hird, K. E. F. Hobbs, D. M. Holmes, Sonia M. Holmes, A. S. Horner, B. L. Houghton, Mary W. Houlston, N. M. How, K. E. E. Hubble, B. V. Hudson, Daphne M. Humphreys, P. Humphreys, M. J. Hunter, Monica P. Hunter, E. J. Igwe, R.-K. R. Innes, H. G. James, I. M. James, M. L. James, W. F. Jaworski, Jill D. McK. Jeffery, R. W. John, B. D. Jones, B. C. Jones, D. A. Jones, Pamela M. Jones, T. M. B. Jones, D. L. Julier, C. P. Juniper, B. Kell, P. Kelly, Margaret L. Kemball, R. C. Kennedy, Helena J. T. Kilkenny, Elizabeth S. Kitchin, D. N. Landon, D. A. H. Langman, J. V. Lee, S. C. Lee, Joan M. Leese, Eva Lester, Eva H. Letchner, A. Levine, E. A. Lewis, D. J. Lightman, C. C. Lim, J. D. Lloyd-Still, Margaret H. Lucy, J. S. P. Lumley, L. Lupin, M. P. McBrien, Patricia M. McCormack, S. J. McDonald, Leonie M. McEwen, M. B. J. McGrath, S. McHardy-Young, Marion MacLellan, M. T. MacMahon, H. B. McMichael, Margaret R. McMinn, I. F. Macrae, N. C. Malcolm, B. M. Male, Rosamund H. Mansfield, D. J. Martin, R. C. Martin, R. J. Mason, J. R. Massy, A. W. Matthews, L. S. Mehta, B. S. Michaels, E. H. S. Miles, Joyce M. Miller, A. J. Mitchell, M. Modell, P. R. W. Monahan, M. V. Moriarty, T. S. Morley, A. E. Morris, M. D. R. Morris, Jayne M. Moses, P. J. Muller, J. J. H. Mülnier, M. K. Murphy, J. F. Murray, J. S. Musgrove, A. S. Mushin, D. M. Muzio, May Ning, G. Nuki, Susan T. O'Connor, P. M. Olley, E. G. J. Olsen, M. J. Olver, R. H. Parrott, J. D. Parry, S. M. Patient, E. H. M. Paul, P. C. Pavier, Catherine S. Peckham, P. J. Pegg, M. J. Pemberton, J. A. P. Pettavel, Sally J. Phillips, Dianne E. Philp, D. Pickering, W. Pickvance, J. V. Piper, B. V. Pippet, A. H. Platts, M. S. Ponnampalam, J. A. ff Pope, G. M. Preston, D. I. Orpwood Price, D. Prothero, K. O. Quansah, B. J. Ranscombe, D. Rau, L. M. Razavi, Hazel L. A. Read, A. R. Reece, P. M. Reilly, G. Reiman, P. G. S. Relton, D. A. Reynolds, Felicity J. M. Reynolds, M. T. Reynolds, Janet Riddle, Christine E. Riley, P. A. Riley, A. D. Rogers, Wendy Roles, A. M. Rose, D. M. Ross, M. G. Royle, I. R. Russell, Zillah A. Russell, E. U. Sagay, P. E. A. Savage, J. D. Scott, Jill Sedgley, R. G. F. Ll. Seed, Maria L. Serbrock, P. Sharpstone, D. W. Shedden, A. J. Sheehan, C. M. Signy, G. W. Simonds, Shirley K. M. Sinclair, M. Singh, Jean A. Skinner, D. J. Smith, M. A. B. Sneary, S. S. Soo-, A. O. O. Sorungbe, Joanna South, P. E. Spicer, Gillian P. M. Stalder, Charmian R. L. Stephens, F. B. Stephenson, Patricia S. Stephenson, Anne K. Stewart, Mary Stewart, Hilary Stirland, A. E. Stocks, D. J. Strath, N. H. Sutcliffe, J. E. K. Tabert, D. C. Taylor, M. E. Taylor, R. A. M. Taylor, S. W. C. Taylor, Helen E. B.-L. Tee, R. S. Terry, C. H. C. Thomas, A. J. Thompson, J. Thomsitt, Ada A. Thornton, R. H. Tipton, P. M. J. Tombleson, D. A. Toms, L. N. Travis, R. R. Trayner, K. Ll. K. Trick, Irene J. Tufft, Florence M. Turner, W. Ursell, Margaret R. A. Utidjian, B. Vernon-Roberts, J. A. S. Vick, Dorothy I. Vollum, B. L. Walman, B. A. Walron, A. E. Walker, Judith G. Walker, K. A. Walker, P. I. Ward, D. J. Warren, W. D. N. Watson, J. L. Wearn, P. C. Weaver, B. R. Webster, F. O. Wells, Tessa Westcott, Myra Wharf, W. F. White, Kyra A. Williams, N. Williamson, R. A. G. d'E. Willoughby, B. P. G. Windsor, M. S. Wirk, J. D. Wonham, Bridget M. Wood, Ann P. Woolley-Hart, Adeline Yen

[1]With honours. [2]Distinguished in pathology. [3]Distinguished in medicine. [4]Distinguished in applied pharmacology and therapeutics. [5]Distinguished in surgery. [6]Distinguished in obstetrics and gynaecology.

UNIVERSITY OF BIRMINGHAM

The following have been appointed representatives of the University on the bodies indicated in parentheses: Professor T. McKeown and Professor J. W. Orr (Regional Cancer (Co-ordinating) Committee); Professor A. L. d'Abreu, Professor W. Melville Arnott, Professor T. McKeown, and Dr. A. G. W. Whitfield (Standing Joint Committee of the University, the United Birmingham Hospitals, and the Birmingham Regional Hospital Board); Sir Arthur Thomson (Faculty of the History of Medicine and Pharmacy).

The following have been promoted to senior lectureships in the subjects indicated in parentheses from October 1, 1960: Dr. D. A. Heath (Pathology) and Dr. B. D. Bower (Paediatrics and Child Health).

Titles have been conferred as follows: Reader in Social Medicine on Dr. C. R. Lowe, Senior Lecturer in Social Medicine; Honorary Reader in Medicine on Dr. J. M. French, Honorary Senior Lecturer in Medicine, and a member of the external scientific staff of the Medical Research Council; Honorary Lecturer in the Department of Experimental Pathology on Dr. J. P. Bull, Director of the Medical Research Council Industrial Injuries and Burns Research Unit, Birmingham Accident Hospital.

The board of governors of the United Birmingham Hospitals has granted honorary status to the following members of staff: Dr. P. W. Dykes, Lecturer in Experimental Pathology, as Honorary Research Associate in Medicine and Radiotherapy; Dr. June M. Raine, University Research Fellow in Medicine, as Honorary Research Associate in Medicine; Dr. C. T. G. Flear, University Research Fellow, as Honorary Assistant Research Associate in Medicine; Dr. S. C. Melnick, University Research Fellow, as Honorary Research Associate in Medicine.

Dr. Sylvia J. Darke, who is working in the Department of Experimental Pathology supported by a grant from the Medical Research Council, and Dr. J. H. Jones, Registrar in the Metabolic Unit at Little Bromwich Hospital, have been given the title of University Research Fellow.

The title of University Clinical Lecturer has been granted to Mr. L. D. Abrams, part-time Consultant Thoracic Surgeon, and Dr. J. L. Whitby, Consultant Bacteriologist, United Birmingham Hospitals.

Mr. F. C. Walker has been appointed Clinical Lecturer in the Department of Surgery from March 1, 1960, and Dr. R. F. Reynolds temporary Lecturer in Anatomy from January 1 to September 30, 1960.

Vital Statistics

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in April was 70, compared with 99 in the previous month and 89 in April, 1959.

The numbers of cases of industrial diseases in the United Kingdom reported during April were as follows: lead poisoning 8, mercurial poisoning 1, aniline poisoning 2, anthrax 1, epitheliomatous ulceration 6, chrome ulceration 35; total 53. There were no deaths.

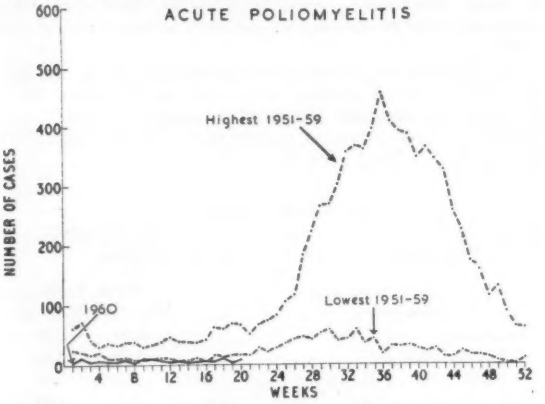
Infectious Diseases

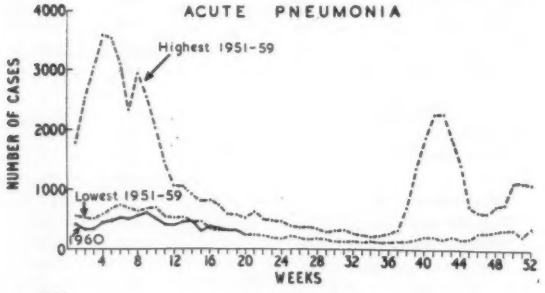
Areas where numbers of notifications were high in the latest two weeks for which figures are available.

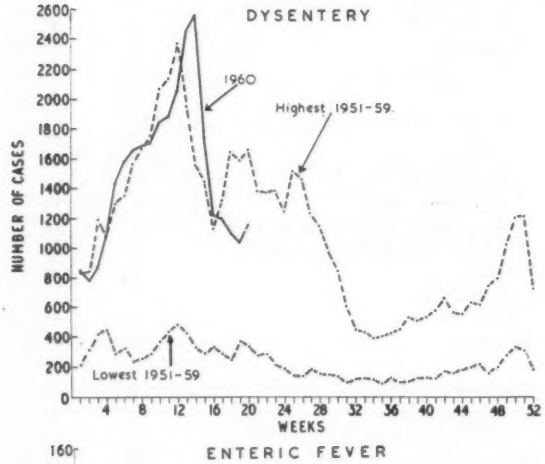
	Week Ending May 14	Week Ending May 21
Measles		
Lancashire	649	**649**
Liverpool C.B.	159	**210**
Manchester C.B.	80	**94**
Leicestershire	66	**100**
Leicester C.B.	40	**82**
Nottinghamshire	80	**129**
Nottingham C.B.	42	**95**
Dysentery		
Durham	31	**41**
West Hartlepool C.B.	2	**16**
Essex	73	**88**
West Ham C.B.	20	**17**
Epping U.D.	0	**10**
Walthamstow M.B.	0	**12**
Epping and Ongar R.D.	0	**10**
Gloucestershire	18	**20**
Bristol C.B.	11	**19**
Hampshire	26	**26**
Portsmouth C.B.	10	**10**
Hertfordshire	14	**29**
Welwyn Garden City U.D.	9	**10**
Lancashire	213	**219**
Liverpool C.B.	35	**29**
Preston C.B.	1	**18**
Accrington M.B.	13	**14**
Morecambe and Heysham M.B.	15	**16**
Swinton and Pendlebury M.B.	7	**10**
London	129	**141**
Bermondsey	9	**11**
Islington	26	**44**
Middlesex	57	**40**
Norfolk	64	**72**
Norwich C.B.	41	**46**
Nottinghamshire	31	**30**
Nottingham C.B.	13	**13**
Warwickshire	20	**24**
Birmingham C.B.	14	**15**
Yorkshire North Riding	10	**26**
Middlesbrough C.B.	3	**11**
Yorkshire West Riding	81	**122**
Bradford C.B.	23	**23**
Leeds C.B.	22	**14**
Sheffield C.B.	10	**32**
Glamorganshire	25	**18**
Llwchwr U.D.	0	**10**
Glasgow	126	**110**

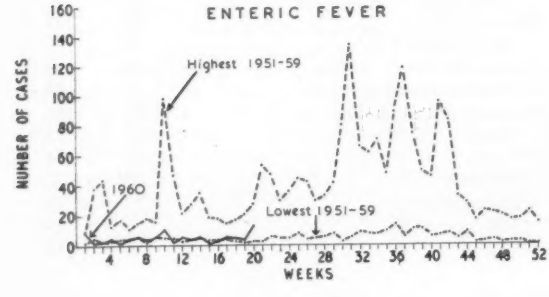
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **May 14** (No. 19) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	1	0	1	0		3	1	0	0	
Dysentery ..	1,038	129	227	18	4	1,067	93	322	7	
Encephalitis, acute	0	0	0	0		2	0		0	
Enteric fever:										
Typhoid ..	2	0	0	0	1	4	1	6	0	
Paratyphoid ..	2	0	0	0		3	1	5(B)	0	
Food-poisoning ..	156	33	15	1		244	70	10	0	
Infective enteritis or diarrhoea under 2 years				16	25				10	
Measles*	1,749	93	42	5	12	18,195	719	445	424	
Meningococcal infection	15	1	9	4		24	3	11	1	
Ophthalmia neonatorum	24	2	3	0		23	7	12	0	
Pneumonia† ..	290	9	187	6	2	336	18	198	9	
Poliomyelitis, acute:										
Paralytic ..	1	0	1	1	4	19	7	1	1	
Non-paralytic	2	0	1			16	4	2		
Puerperal fever§ ..	178	24	13	2		223	41	7	0	
Scarlet fever ..	589	30	55	16	17	997	46	86	20	
Tuberculosis:										
Respiratory ..	457	43	79	17		567	94	88	15	
Non-respiratory	62	7	10	5		71	12	14	1	
Whooping-cough	1,362	121	266	1	39	611	28	84	22	

DEATHS	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	0	0	0	0	0
Dysentery ..	1	1	1	0		4	1		1	
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	10	0	1	0	0	4	0	3	0	1
Influenza	19	1	6	0	0	23	0	0	3	1
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia ..	601	39	18	14	10	500	36	16	20	12
Poliomyelitis, acute	1	0		0	0	3	1		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	68	6	4	2	1	65	5	4	0	5
Non-respiratory		0	0	0	0		1	0	0	1
Whooping-cough	0	0	1	0	0	0	0	0	0	0
Deaths 0–1 year ..	306	28	29	7	13	341	31	26	6	6
Deaths (excluding stillbirths) ..	10,214	825	600	128	200	9,626	725	558	128	161
LIVE BIRTHS ..	16,003	1333	1048	282	459	15,289	1310	132	282	468
STILLBIRTHS ..	308	28	30			334	18	19		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Transistor Hearing-aids

A start will soon be made on issuing Medresco transistor hearing-aids to adults. Up till now they have been supplied only to children and to war pensioners with certain disabilities. The Minister of Health, Mr. D. WALKER SMITH, has suggested the following additional order of priorities: (1) adults who received a transistor aid as children and require a replacement, (2) the deaf-blind, (3) those who are dependent on a hearing-aid for employment and are severely handicapped in their work by a valve aid, (4) mothers with young children, and those who, because of physical disability, cannot make full use of a valve aid.

"British Medical Students' Journal"

"Excellent as the *B.M.S.J.* is in many respects," says P.B., of Birmingham, "it lacks one essential feature . . . what it really needs to give it mass appeal is an 'Advice Column.' Only then can we hope for a circulation to rival the national 'dailies.'"

As Embolus discusses the problems of the married medical student on another page of the *B.M.S.J.'s* summer issue—suggesting that "the State should accept the necessity for extra annual holidays in which it may expect housemen to woo, registrars to propose, senior registrars to wed, junior consultants to think about things, and so on . . ."—P. B. is probably right. Apart from considering the problems provoked by the spring, the *B.M.S.J.* includes articles on "The Missionary Doctor" by Dr. G. V. THRES, the Medical Missions Secretary of the Society for the Propagation of the Gospel, and on many other topics ranging from the W.H.O. malaria campaign to climbing in the Cuillins, and from dysphagia to the divided city of Berlin. (Price: B.M.S.A. members 6d., others 1s., *B.M.S.J.*, B.M.A. House, Tavistock Square, London, W.C.1.)

New Medical Teaching Centre for Wales

The £5,000 prize in a competition to design the £7m. University Hospital of Wales, to be built at Heath, Cardiff, has been won by S. W. MILBURN and Partners, of Sunderland. There were 40 entries.

The whole project is said to be unique in the history of hospital building in this country in that for the first time the hospital and the medical school will be planned and built as an integrated whole from the beginning. There will be a helicopter site over a covered car park—marked (1) on the ground plan, a dental hospital and school (3), a medical school (4), a maternity block (5), a general hospital block (6), a paediatric block (7), out-patients and casualty departments (8), and residential and recreational accommodation for doctors (2), nurses (12), medical students (13), and staff. The main structure, of steel and glass, overlooks an area of parkland set round a small lake. The nurses' dining-hall (10) is built over the lake and is reached by a flyover bridge which is also linked to the recreation hall (11). There will be, initially, 650 beds, capable of extension to 800, and 65 medical students a year from the Welsh National School of Medicine will be given their clinical training at the hospital. The dental school will take 50 students a year, and, because of the pressing need for dentists, the dental school and hospital will be part of the first stage to be built. It is not yet known when work will begin, but once it does the first stage should be completed by 1964. The assessors have commented on the winning design's spaciousness, dignity, simplicity, and freedom, and they say that the "much desired integration of medical school and hospital is imaginatively achieved with seemingly effortless ease."

Formation of Registry of Diseases of Trophoblast

The Royal College of Obstetricians and Gynaecologists, with the support of the Pathological Society of Great Britain and Ireland and the Association of Clinical Pathologists, has decided to create a subdivision of its Tumour Registry for Diseases of Trophoblast (special registrar, Dr. W. W. PARK). Material from evident cases of chorioncarcinoma and hydatidiform mole is wanted, and the registrars would particularly welcome material from "borderline" cases. Clinicians and pathologists are invited to submit any or all of the following material: clinical data (on forms to be supplied); pathological tissue; paraffin blocks; histological sections. All communications should be sent to the Registrars, the Tumour Registry, Royal College of Obstetricians and Gynaecologists, Nuffield College, Sussex Place, Regent's Park, London, N.W.1.

Medical Protection Society

Sir ERNEST ROCK CARLING, president of the Medical Protection Society, welcomed a large number of distinguished guests at a reception held in the Society's new house in Hallam Street on May 25. This house, No. 50, has recently been vacated by the General Dental Council and is next door to the General Medical Council. Although the exterior is plain, the interior has an eighteenth century elegance, and the building is scheduled by the L.C.C. as one of architectural merit. Guests at the reception had the opportunity of admiring the portrait of Sir Ernest Rock Carling commissioned by the Society from Major A. C. Davidson-Houston.

Oxford Graduates' Medical Club

All graduates of the University of Oxford who have qualified in medicine are eligible to join the Oxford Graduates' Medical Club. It dines twice a year, the Winter Dinner being held in London and the Summer Dinner in an Oxford College. The life membership subscription is one guinea, and application for membership should be made to Miss JOSEPHINE BARNES, 7, Wimpole Street, London, W.1.

Carmichael Prize Essay, 1961

The Royal College of Surgeons in Ireland will award prizes of £150 and £100 for essays on subjects prescribed by the late Mr. RICHARD CARMICHAEL in which suggestions may be made "respecting the improvement of the [medical] profession, with the view of rendering it more useful to the public, and a more respectable body than it is at present." Details of the competition may be obtained from Professor W. N. RAE, Royal College of Surgeons in Ireland, Dublin. Closing date March, 1961.

Chair of Bacteriology, London University

Dr. R. E. O. WILLIAMS, director of the Streptococcus, Staphylococcus, and Air Hygiene Reference Laboratories, Colindale, has been appointed to the University chair of bacteriology, tenable at St. Mary's Hospital Medical School.

Dr. Williams was educated at University College, London, and University College Hospital, graduated M.B. in 1940, proceeded to the M.D. in 1945, and was admitted to the M.R.C.P. in 1960. He worked from 1942 to 1946 in the Medical Research Council Wound Infection Unit in the Birmingham Accident Hospital. Since 1946 he has been a member of the staff of the Public Health Laboratory Service, and has held his present post

The winning design in the competition for a new University Hospital of Wales.

since 1949. His research work has been concerned with the bacteriology of streptococci and staphylococci, and with the epidemiology of streptococcal and staphylococcal infections, especially in hospitals.

Provident Scheme for B.M.A. Members

The Group Scheme for B.M.A. members proposed by the Hospital Service Plan is being recommended by Council for approval by the Annual Representative Meeting at Torquay later this month (see Supplementary Annual Report of Council, *Supplement*, April 23, p. 220). If approved by the A.R.M., details of the scheme will be sent by post to every member of the B.M.A. in the United Kingdom.

Royal College of Nursing President

Miss M. J. SMYTH, O.B.E., has been elected President of the Royal College of Nursing for 1960–1. Formerly matron of St. Thomas' Hospital and superintendent of the Nightingale Training School, she has been chairman of the General Nursing Council for England and Wales since 1955.

"Family Doctor"

The June issue of *Family Doctor* is now on sale, price 1s. 6d. It includes articles on advances in heart surgery by Sir RUSSELL BROCK and on motivation research by Professor H. J. EYSENCK.

In Brief . . .

The 30,000 native inhabitants of the Fore District in New Guinea are to be confined to their tribal area of 884 square miles in the eastern highlands in an attempt to check the spread of kuru, a degenerative disease now believed to be genetically determined. An account of the disease was given in the *B.M.J.*, December 21, 1947, p. 1480.

People in the News

Dr. H. B. TURBOTT, the Director-General of Health of New Zealand, who was recently elected president of the Thirteenth World Health Assembly, is studying medical services and visiting hospitals in the United Kingdom.

COMING EVENTS

Faculty of Radiologists.—Annual meeting June 10–11. Middlesex Hospital Medical School, Cleveland Street, London, W.1. Knox Lecture, June 10, 4.30 p.m.: Professor B. W. WINDEYER, "The Medical Profession and the Nuclear Age." Admission free.

Institute of Child Health London University.—Lecture by Dr. R. S. PAINE (Department of Neurology, Children's Medical Center, Boston): "Neurological Examination of the Newborn Infant," June 10, 5 p.m., New Lecture Theatre, The Hospital for Sick Children, Great Ormond Street, London, W.C.1. Admission free.

St. Cyres Lecture, Institute of Cardiology.—Sir RUSSELL BROCK, "The Surgical Treatment of Pulmonary Stenosis"; June 17, 5 p.m., Barnes Hall, Royal Society of Medicine, 1, Wimpole Street, London, W.1.

11th Victor Horsley Memorial Lecture.—Professor N. M. DOTT (professor of neurological surgery, Edinburgh University): "Brain, Movement, and Time." Chairman: Sir ARTHUR THOMSON. June 24, 11 a.m., Great Hall, B.M.A. House, Tavistock Square, London, W.C.1.

Nursery School Association.—National conference: July 1, 9.30 a.m. to 4.30 p.m., William Beveridge Hall, Senate House, Malet Street, London, W.C.1. Speakers: Mr. W. O. WALL, Ph.D. (director, National Foundation for Educational Research), "The Enrichment of Childhood"; Miss ANNA FREUD, LL.D. (director, Hampstead Child Guidance Clinic), "Why Children Go Wrong." Applications to Conference Secretary, Nursery School Association, 1, Park Crescent, London, W.1.

Oxford Graduates' Medical Club will hold their Summer Dinner in St. Peter's Hall, Oxford, on Saturday, July 9. Details from Dr. R. BRYCE-SMITH, Department of Anaesthetics, Radcliffe Infirmary, Oxford.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Tuesday, June 7

BELMONT HOSPITAL CLINICAL SOCIETY.—8 p.m., Baroness Wootton of Abinger: Future of Responsibility.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. A. Rook: Skin Sensitivity to Plants.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute, 5 p.m., Dr. P. M. F. Bishop: Sex Hormones During Pregnancy.

Wednesday, June 8

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. A. Tickner: Fats in Relation to Skin Disease.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. N. R. Barrett: Some Surgical Aspects of Dysphagia.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—6 p.m., Dr. E. H. Maier (Vienna): Changes in the Mucosa in Nasal Allergy.
LONDON UNIVERSITY.—At King's College, Strand, W.C., 5.30 p.m., special university lecture in biophysics by Dr. A. J. Dalton (Bethesda, U.S.A.): Electron Microscopic Studies on a Series of Plasma Cell Tumours in Mice.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. W. E. van Heyningen: Cynical Spasm.
ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH.—5 p.m., Lister Fellowship Lecture by Professor Robert Cruickshank: Measurements in Medicine.
YORKSHIRE SOCIETY OF ANAESTHETISTS.—At General Infirmary at Leeds, 8.30 p.m., Dr. Shila Ransom: Role of the Anaesthetist in the Obstetric Unit.

Thursday, June 9

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Primary Skin Cancer, Clinical and Pathological.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—6 p.m., Dr. E. H. Maier (Vienna): Laryngectomy with Preservation of the Air Passages.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Queen Charlotte's Hospital, 4.30 p.m., Professor J. Chassar Moir: Technique and the Place of Caesarean Section in Present-day Obstetric Practice.
LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—3 p.m., visit to Lullingstone Roman Villa, Eynsford, Kent.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. David Bates (Montreal): Place of Respiratory Function Tests in the Treatment of Patients with Chest Disease.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor P. M. Weston: Pathology and Treatment of Urethral Stricture and its Complications in Jamaica.
ROYAL SOCIETY OF HEALTH.—At Salford Grammar School, 10 a.m., symposium: Team-work in the Health Services. Speakers, Dr. A. A. Leigh, Miss M. Thwaites, R.S.C.N., S.R.N., Miss V. E. Langridge, S.R.N., Miss N. Perry, S.R.N., Miss B. Chadwick, and Mr. Ronald Cooke.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., postgraduate demonstration by Dr. Denis Williams: Neurology.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Dr. S. J. Bach: Metabolic Fate of Protein-Nitrogen in the Mammal—(2) Biosynthesis of Urea.

Friday, June 10

INSTITUTE OF CHILD HEALTH.—5 p.m., Dr. R. S. Paine (Massachusetts): Neurological Examination of the Newborn Infant.
●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. D. I. Williams: clinical demonstration
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. L. Livingstone: clinical demonstration
INSTITUTE OF NEUROLOGY.—4.30 p.m., Dr. William Gooddy: Physical Basis of the Time Sense.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Chelsea Hospital for Women, 4.30 p.m., Mr. J. Stallworthy: Myomectomy.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Mr. R. T. Johnson: Surgical Aspects of Infection of the Nervous System.

Saturday, June 11

NORTH OF ENGLAND OTOLARYNGOLOGICAL SOCIETY.—At Carlisle, 2 p.m., combined meeting with Scottish Otolaryngological Society.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Leese.—On May 14, 1960, to Eileen (formerly Spence) and William L. B. Leese, a daughter—Alison Margaret.

Sweetnam.—On May 19, 1960, at City General Hospital, Stoke-upon-Trent, Staffs, to Michael and Elizabeth Sweetnam, a son.

DEATHS

Bennett.—On May 16, 1960, at Chernocke, Maxwell Road, Canford Cliffs, Dorset, Francis Grey Bennett, L.M.S.S.A., aged 87.

Fraser.—On May 15, 1960, Agnes Renton Fraser (formerly Robson), M.B., Ch.B.

Holland.—On May 15, 1960, at 34, Station Road, Hinckley, Leics, Charles Kenneth Holland, M.B., Ch.B., aged 53.

Jurewicz.—On May 16, 1960, at 102, Rye Hill, Newcastle upon Tyne, Northumberland, Wiktor Jurewicz, M.B., Ch.B., aged 50.

Kane.—On May 20, 1960, at King's College Hospital, Michael Harry Kirkpatrick Kane, *M.C.*, M.D., M.R.C.P., of Point House, Thorpe, Norwich, Norfolk, aged 67.

Murray.—On May 16, 1960, at St. Annes-on-Sea Hospital, John Kennedy Murray, M.B., Ch.B., of 300, Clifton Drive South, St. Annes-on-Sea, Lancs, formerly of Winchcombe, Glos, aged 65.

Peterkin.—On May 19, 1960, in hospital, James Harold Stuart Peterkin, *M.C.*, M.B., Ch.B., of Marine House, Hornsea, Yorks.

Pickels.—On May 16, 1960, in a nursing-home, St. Leonards-on-Sea, Sussex, Joseph Arthur Pickels, M.B., B.S., D.P.H., formerly of Crowhurst, Sussex, late of Accra, Gold Coast, aged 92.

Stoddart.—On May 19, 1960, at Woodend Hospital, Aberdeen, George Stoddart M.B., Ch.B., of 9, Louisville Avenue, Aberdeen, late of Clapham, London, S.W.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Mongol in the Family

Q.—*A young couple with a mongol child 18 months old are expecting another baby. Devoted though they are to the mongol, would it be better to put it into a residential home for the sake of the second, presumably normal, child? Is there any consensus of opinion on this problem? Money, in this case, is not an obstacle.*

A.—There are many variable factors in such a situation, and no answer can be given which will cover all cases. On the whole, children with mongolism do better at home. Therefore, from the standpoint of the child itself it is better for it to remain at home. There is no reason why the care of the child with mongolism should at this stage interfere with the care of the new baby, particularly as the finances of the parents are adequate. In effect, the mother would be caring for one presumably normal newborn baby and another one with a mental age of, say, 6 to 9 months. This is a common situation with which many mothers cope. If the parents are prepared to do so, they should be encouraged to keep both children at least for several years to see how matters develop. If the situation becomes difficult in the course of time they could always then ask for institutional care. Something will depend on the age of the parents and their professional and social commitments. Since this couple are young they should have no great difficulty in managing the two children. There is a wide range of intelligence in mongolism; this will also influence the matter. If the child is near to the educationally subnormal range then the mother will have the reward of seeing obvious progress in the child's development. Whereas if the affected child is in the idiot range the mother may press for institutional care at an earlier age, since there will be very limited response to her efforts at training and caring for the child. There is no reason to suppose that the presence of the abnormal child in the family will in any way prejudice the development of the normal child in such a situation unless, of course, as occasionally happens, the mother devotes an undue share of her attention to the affected offspring. A little common sense will usually avoid this. In a few years' time the child with mongolism should be able to attend a special training school or occupation centre daily, which would be a great assistance to the mother.

Anticoagulants and Peptic Ulcer

Q.—*A man aged 40 had a coronary thrombosis 18 months ago and has had phenindione since that time. Now he has developed an active duodenal ulcer. What is the correct procedure?*

A.—One of two courses may be adopted. Either the phenindione may be stopped and the ulcer treated in the usual way, or the anticoagulant may be continued but the patient treated for his ulcer in hospital (or similar circumstances), with frequent checks on prothrombin time and examination of stools for occult blood. If the former course is chosen, the anticoagulant should be discontinued gradually.

It is impossible to be more precise without knowing more about the patient. How many attacks of coronary occlusion has he had? Is he now free of symptoms, or does he have angina or symptoms of congestive heart failure? Has he a strong family history of coronary artery disease, and/or a high blood cholesterol? Has the duodenal ulcer bled?

If he is symptomless, with normal cardiac function, and no family history, then, since he has already had 18 months' anticoagulant therapy, it would be the wiser course to stop it at this point. However, if the patient still has symptoms of ischaemic heart disease, or has had a recent infarct, then the risks of discontinuing anticoagulant therapy must be balanced against the risk of bleeding from the ulcer if such therapy is continued.

Climate and Rheumatoid Arthritis

Q.—*Is there any significant connexion between climate and the progression of rheumatoid arthritis?*

A.—There are no definite data proving that any particular kind of climate affects the progression of rheumatoid arthritis. Although most rheumatoid sufferers feel worse in damp, cold weather, some prefer it and do less well in a hot and dry climate. Most aches and pains are worse on dull, grey days; pain tolerance may be affected by lowered spirits. It is unwise to recommend a complete change of work and habitation to a patient in the hope that his rheumatoid arthritis might be improved; it might or might not be. Although in a warm, dry climate most sufferers feel better, the disease often, perhaps usually, progresses much as before, though symptoms may be less troublesome. All other factors, personal, economic, and domestic, have to be taken into consideration also: climate is only one of many.

Athlete's Foot

Q.—*What is a speedy treatment for chronic athlete's foot?*

A.—Chronic athlete's foot which consists only in interdigital scaling and maceration can be *quickly* remedied by the application twice daily of Whitfield's ointment or of most of the proprietary fungicidal applications. It is not certain whether this is also an *efficient* treatment. Relapses are very common indeed, and it is not easy to decide whether they are recurrences of the same infection or fresh infections. Whatever the treatment of athlete's foot, recurrences are so frequent that it is doubtful whether any method can be called efficient. There is good reason to suppose that many of these relapses result because the fungus remains on the feet without producing lesions until heat and maceration are suitable for its growth. If this is so then relapses will probably result from conditions of heat and moisture and fresh infection is not necessary.

Many cases of chronic athlete's foot are accompanied by a nail involvement. When this is so griseofulvin given by mouth for a period of five or six months is the most promising treatment.

If the term chronic athlete's foot is intended also to include eczematous eruptions, treatment is more difficult. Measures directed against the eczematous process may be more important than fungicides. There is no speedy and efficient way of treating the disease in this phase.

Adrenaline and Quinine

Q.—*Some authorities warn against the use of adrenaline in the treatment of hypotension after rapid intravenous injection of quinine. Why is this?*

A.—The circulatory collapse which may follow the intravenous injection of quinine is due partly to the depressant effect of the drug on the heart and partly to peripheral vasodilatation. It is related to the amount of quinine given and to the rapidity of administration, and it is more likely to occur in patients who are emaciated and seriously ill. Both Goodman and Gilman[1] and Findlay[2] recommend adrenaline as an effective agent for the prevention and treatment of the hypotension caused by the intravenous injection of quinine. They quote the experimental work of Dreisbach,[3] who found both in rabbits and in cats that adrenaline was the only drug which consistently antagonized the blood-pressure-lowering effect of quinine, and that it did so even in the presence of shock, haemorrhage, and hyperthermia. Grollman,[4] on the other hand, states

that quinine antagonizes the pressor effects of adrenaline and that adrenaline fails to cause a rise in blood-pressure after the intravenous injection of quinine. The reason for the warnings against the use of adrenaline is no doubt that several instances of ventricular fibrillation have been recorded after the intravenous injection of quinine in patients who are ill-nourished and heavily infected with malaria, and it is known that adrenaline, particularly when given intravenously, is also apt to cause ventricular fibrillation.

REFERENCES

1 Goodman, L. S., and Gilman, A. G., *The Pharmacological Basis of Therapeutics*, second edition, 1955. Macmillan, New York.
2 Findlay, G. M., *Recent Advances in Chemotherapy*, third edition, 1951. J. and A. Churchill Ltd., London.
3 Dreisbach, R. H., *J. Pharmacol. exp. Therap.*, 1949, **95**, 347.
4 Grollman, A., *Pharmacology and Therapeutics*, third edition, 1958. Henry Kimpton, London.

Incomplete Immunization

Q.—*A child inadvertently received three injections of 0.5 ml. tetanus toxoid instead of 1 ml. Is it now necessary to give a course of three injections of 1 ml.? In the meantime, would it be wise to give A.T.S. in the event of wounding?*

A.—To some extent the age of the child is of importance: because of body-weight, the younger the child the more satisfactory might be the immunological response to three injections of 0.5 ml. tetanus toxoid. The intervals between the three doses are not mentioned, but presumably the first two doses were spaced by about six weeks, and the second and third doses by six to twelve months, which is the usual recommendation in this country.[1] Although there is considerable variation in the responses of different individuals, such a course would be likely to produce a useful degree of protection, which, however, might not be so durable as one would wish. One injection of 1 ml. of toxoid should be given to make good any possible deficiency resulting from the relatively low dosage; it is not necessary to give another full course of injections. In the event of wounding, tetanus antitoxin would not be required, 1 ml. of toxoid being all that would be necessary. A further reinforcing dose of toxoid is indicated after an interval of five years. The importance of medical records, which would be carried on the person so as to be immediately available, is particularly emphasized in a case such as this.

REFERENCE

1 *Proceedings of a Symposium on Immunization in Childhood*, 1960. E. and S. Livingstone, Edinburgh and London.

Rats in the Sugar

Q.—*What means may safely be used to suppress rat infestation in a storage depot for sugar? There is a danger of contamination of the sugar if poison is used, either from decomposing dead rats or from the poison itself. Cats have been tried, but they resign from the job very quickly.*

A.—Poisoning is the only effective remedy if the infestation is a heavy one. "Warfarin" in liquid form would be safe and effective. If the sugar was properly stacked on racks raised from the floor there would be no danger of contamination. If it is not so stacked this ought to be done before attempting to eradicate the rats.

The Pest Infestation Division of the Ministry of Agriculture, Fisheries, and Food would probably be pleased to help.

Physiotherapy in Chronic Chest Disease

Q.—*What physiotherapy, including exercises, improves ventilation in chronic chest disease?*

A.—Most chronic chest cases, when secretions are present, benefit greatly from postural drainage, with percussion or shaking, prior to breathing exercises. Diaphragmatic breathing is then taught with insistence on a relaxed upper chest and accessory breathing muscles, while movement takes place "around the waist." Lateral basal expansion, against the hand or a band, and done singly, will help to improve rib excursion.

Easy mobility exercises for loosening up the chest wall—i.e., rhythmical side flexions, trunk twistings with arm flingings, back lying, hip rolling, etc.—help to make a rigid chest move with greater ease. Since stairs usually present a big problem to these patients, it is helpful to them to be taught under a physiotherapist's supervision how to control their breathing on a test flight until they can tackle the climb with some confidence. Obviously, the amount of activity that can be given to a patient, and the amount of improvement, must depend on the amount of lung damage present.

Haemophilia in Jews

Q.—*How common is haemophilia among Jews? Presumably three millenniums of ritual circumcision must have eliminated most of the males who might have been expected to pass the trait on through their daughters?*

A.—So far as I know there is no information about the incidence of haemophilia among different ethnic groups. I do not think that anyone has collected this information specially. So far as I know there are no orthodox Jewish patients among our series of about 200 haemophilic patients, because the question of circumcision would naturally have arisen. But I have not routinely asked about the patients' ancestors from this point of view. So the supposition in the question may very well be true.

I have, however, five probable cases of plasma thromboplastin antecedent deficiency (P.T.A.), all of whom are of Jewish descent. I don't know whether other workers have made a similar observation. This defect is relatively mild in comparison with haemophilia, and infants would be likely to survive circumcision.

Chicken-pox in Pregnancy

Q.—*Is there a possibility of danger to the foetus when a mother develops chicken-pox in the third month of pregnancy?*

A.—In a recent paper[1] it was stated that "for the present it must be concluded that there is no evidence to show that diseases such as measles, chicken-pox, herpes zoster, mumps, scarlet fever, poliomyelitis, and infective hepatitis significantly distort foetal development, even when contracted early in pregnancy. The position in regard to influenza is uncertain. The risk of rubella, however, is real."

REFERENCE

1 Jeffcoate, T. N. A., *Brit. med. J.*, 1960, **1**, 586.

Correction.—We regret that two photographs were inadvertently misplaced in the advertisement of "phisohex" (Bayer Products Ltd.) in the *Journal* of April 30 (advertisement pp. 13–14). The last two culture plates illustrating tests carried out by the dental surgeon should be transposed to each other's position.

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

Refresher Course for General Practitioners, Volume 3 (26s. 9d.).
Clinical Pathology in General Practice (22s. 3d.).
Any Questions?, Volume 3 (8s. 3d.).

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